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Frank Norman Wilson

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THE RECENT DEATH of Frank N. Wilson, after an illness of nearly four years, brought to an end the career of one of the greatest scientists of our time. The news that Dr. Wilson had passed away suddenly, following an acute coronary thrombosis, came from the Wilson farm near Stockbridge, Michigan, early on the morning of September 11, bringing sadness and a feeling of great personal loss to his many friends, associates, both past and present, and to his students all over the world.

It should be recalled with a sense of satisfaction that Dr. Wilson's outstanding work in his field was recognized, and tribute was paid to him during the year of his sixtieth birthday, well before his death. The issue of CIRCULATION of July 1950 was dedicated to him. One of his oldest friends, Dr. Samuel A. Levine, in the foreword, summarized his career and pointed out the unusual abilities and traits of character that led to his success. This recognition was followed by a similar appreciation written by Dr. George R. Herrmann, which appeared in the *American Heart Journal* of November 1950. These honors were climaxed by the award of the Gold Heart Medal of the American Heart Association at the time of their annual meeting in June 1951. Although never demonstrative, Dr. Wilson felt these tokens of respect and appreciation very deeply. It was characteristic of the man that, in the letter he wrote to Dr. Katz accepting the Medal, he stated that much of the credit for his contributions should be given to his associates. Those of us who worked with Dr. Wilson know how completely he dominated and was responsible for most of the studies that were made in his laboratory. He wrote many papers on which his name did not appear as an author, and his associates often received credit for work that was originated and carried on to completion by the Chief.

It is not possible here to mention even in outline form the great contributions made by Dr. Wilson in the field of electrocardiography. Fortunately, this is unnecessary if the unusual character of his research activities is understood. No investigator in recent years has done more to provide a firm and fundamental foundation in a field of scientific endeavor than has Dr. Wilson in the field of electrocardiography. All of his work in this domain was done primarily in an effort to explain why certain changes appear in electrocardiograms under particular circumstances, and never was he satisfied with the purely descriptive approach that has been used so often in electrocardiographic research. Although some of his work, particularly early studies, were concerned with the cardiac arrhythmias and other allied subjects, much of his research was devoted to study of the ventricular complex, and his contributions in connection with bundle branch block, myocardial infarction, ventricular hypertrophy and abnormalities of the T waves provide the basis for much of our current knowledge of these conditions. His long familiarity with bioelectric phenomena, his keen and inquiring mind and his ability to use mathematics enabled him to devise the central terminal arrangement and, one of the most ingenious and basic concepts in the field of electrocardiography, the ventricular gradient. The former is now generally conceded to provide an indifferent electrode

with small potential variations throughout the cycle, and without it the whole field of unipolar electrocardiography, as we know it today, would be nonexistent.

Important though Dr. Wilson's papers and tangible contributions have been, his influence as a teacher and as an exponent of sane and conservative interpretation of electrocardiograms will probably be of greater lasting value. His profound knowledge of the electrical phenomena underlying the electrocardiogram made him acutely aware of the many things apart from heart disease that may alter the records, and he often commented that the more a physician knows about electrocardiography the more conservative his interpretation of the records will be. Much of Dr. Wilson's time in the last years of his active service in the Heart Station was devoted to informal teaching of electrocardiography to doctors who came from all over the world to study in Ann Arbor under him. Although this type of teaching was a constant strain and took time that he would have preferred to use in other ways, he rarely discouraged these activities, since they helped greatly to spread the gospel of careful and conservative interpretation of electrocardiograms. Many of the physicians who studied in the Heart Station now occupy teaching posts in this country or abroad, and all of them regard Dr. Wilson with a respect that is close to reverence.

Although blessed with the finest of minds, an amazing ability to reduce difficult problems to their fundamentals, a great power of concentration which frequently made him quite oblivious of his surroundings, and a dogged persistence which kept him at work until tasks were completed, Dr. Wilson was intensely human and quite devoid of pomp or pretense. He always had time to help others with their problems, and, even in periods of discouragement during his long final illness, his advice and counsel were readily available and freely given. Although Dr. Wilson's life was dedicated primarily to electrocardiography, he had many other interests and hobbies. Both he and Mrs. Wilson loved the country, and for over 20 years had spent more and more of their time at the simple farm near Stockbridge. Here he continued his study of birds, an avocation that began during his association with Sir Thomas Lewis during the first World War, and, from bird photography, his familiarity with optical equipment led to an interest in astronomy, which gave him much pleasure. His life was full, and his accomplishments were great. While his great work was primarily due to his own intellect and character, his wife must not be forgotten. Her devotion and understanding made it possible for Dr. Wilson to carry on and to reach the goals that he sought.

FRANKLIN D. JOHNSTON

The George E. Brown Memorial Lecture

Physiologic Considerations Concerned with the Pathogenesis and Treatment of Obstructive Vascular Disease

By Isaac Starr, M.D.

The therapy for thromboangiitis obliterans advised by George E. Brown and his collaborators in 1928 is taken as a starting point for a discussion of modern conservative measures now properly used in the treatment of peripheral vascular disease of the obstructive type.

THE INVITATION to deliver the *George E. Brown Memorial Lecture*, with which your chairman has honored me, provides an opportunity to attempt something rather different from the ordinary scientific presentation, and I propose to make full use of this opportunity. I have no new research to report to you; although for a while the peripheral vascular field monopolized a great deal of my interest and time, this has not been the case in later years. I am, therefore, attempting the assessment of old knowledge rather than the announcement of new information (a state of mind not infrequently found in those who have no research to report), and you will also find that I have grown old enough to enjoy reminiscences of my younger days. I am, as it were, pausing and looking backward to evaluate the past before turning again to face the future, and, if the truth be known, I think we do far too little of this in American medical science, in which each of us is so likely to be concerned with the details of his own work that those either interested in, or, indeed, capable of taking a broader viewpoint are few indeed.

Of Brown's many contributions I have always been most interested in those summarized in the little book on thromboangiitis obliterans[1] he published together with Dr. Allen and Dr. Mahorner in 1928. The book is an account of a physiologic study of peripheral vascular disease and the effects of treatment upon it, employing methods such as calorimetry and skin temperature, which are still standard today. It is concerned with vasomotor reactions, with securing maximal vasodilatation and with the development of a test based on the ability to secure maximal vasodilatation by which it is hoped to predict the success or failure of sympathectomy. How much that test has been used! In my opinion this book contains most of Brown's best work, although it was published seven years before he died. I suggest, therefore, that we return, as it were, to the year 1928 and study some of the ideas developed in this book and ask ourselves how they differed from those of Brown's predecessors in that field, and how the period of 25 years which has now elapsed has dealt with them, always remembering that it is our purpose, as it was his purpose, to learn so much about the diseases studied that new therapeutic steps will suggest themselves; then, by careful experiment and observation we can determine the value of each new therapeutic method which is suggested.

Conceptions Current Before 1928

Let us recall the background under which Brown was working in the years preceding 1928. At the time he and I were in medical school, clinical medicine in the U. S. was dominated by the great pathologic school of thought, whose primary interest was in the lesions found at necropsy. It was under the aegis of this school that the obstructive lesions of peripheral vascular disease had been discovered and described. As a result of such knowledge when a clinician detected diminution or lack of pulsation in a

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peripheral vessel, he could confidently predict that at necropsy the vessel would be found obstructed by something solid and tangible, by a clot perhaps, by a sclerotic lesion of the vessel's walls, either alone or accompanied by a clot, or possibly by pressure from without. This concentration of thought on the demonstrated arterial obstruction had led to a completely pessimistic therapeutic outlook. The vessel was obstructed and nothing could be done about it; the disease ran its malignant course, more vessels would become involved, the part supplied would suffer increasingly from lack of blood until eventually gangrene was inevitable. So there was only one thing to be done. High and early amputation was the treatment. I recall very well my early initiation into the methods of thought of this school when, as an interne, I ushered a surgical consultant on to the ward and showed him an area of superficial gangrene no bigger than a dime on the toe of an elderly patient who was having a certain amount of pain in his foot, but otherwise seemed in pretty fair condition. The surgeon's reaction was immediate and certain: "This is as great an emergency as any case of appendicitis. The leg must come off. Send him to the operating room immediately and I will take off the leg above the knee as soon as he can be gotten ready." The justification for such extreme measures lay in the experience with gangrene in diabetics before the insulin era, which had shown that, unless surgical treatment was both prompt and radical, the patient went into an acidosis which was quickly followed by death. From this experience the inference had been drawn that any gangrene was highly dangerous to life, a belief that died only slowly in the years which followed the discovery of insulin.

However, soon after that surgeon and I had talked in 1921—and he did take the leg off that afternoon—a new school of thought began to exert its influence on clinical medicine, a school which regarded disease not only from the anatomic but also from the physiologic point of view; and because the physiologic aspects of vascular disease are often amenable to treatment, whereas the anatomic ones are likely to be less so, it soon became possible to regard peripheral vascular disease from a different and more hopeful viewpoint. But old ideas sometimes die hard in medicine and this brings to mind my early struggles when I, a stripling with more laboratory than clinical experience, had the temerity to suggest that amputation might be postponed at least until some conservative measures had been tried and had failed, a position in which I received much encouragement from my chief, Dr. Stengel, who had always had in the back of his mind the feeling that the medical profession was somehow off the track in the peripheral vascular field. Despite his interest and support, things were teetering rather badly for conservative measures when a sudden streak of luck or good fortune turned the tide in my favor, for there came into my possession a consultation written by the then chief professor of surgery in my school, who, visiting a middle aged diabetic patient on my ward with both feet infected and an unhealed wound where a toe had been amputated at another hospital, wrote on the consultation blank, "I advise the amputation of both legs above the knees." Despite the thundering of Jove, I, impudent young fellow that I was, demurred, and was loyally supported by my chief. The course of events fully justified us. The feet healed and although one of them eventually did come to amputation, this was performed over 10 years after the professor of surgery wrote that consultation, and during these years the patient had good use of both of them. Indeed he was still using the remaining leg when last seen in 1952, almost 20 years after the consultation mentioned. After that episode I had nothing but cooperation from the surgeons in my fumbling first attempts at conservative measures based on physiologic principles.

Influence of Sir Thomas Lewis

The person who had most influence on my way of thinking, and without doubt he influenced Brown also, was the Englishman, Sir Thomas Lewis, and I well remember the fascination that his books had for me. The book which summarizes his early work on the peripheral vessels was published in 1926 under the title of "Blood Vessels of the Human Skin and their Responses."[2] In preparation for this

ecture I looked over my old copy of this book, vell worn with much reading and full of my narginal notes. Sir Thomas had been working on this subject for the preceding 11 years and knowledge of what was going on reached this country not only from his publications but also from the many American students whom he nade welcome in his laboratory. These came n large numbers, many doubtless attracted by the vigor of his creative mind, and perhaps some attracted more by his earlier work with the electrocardiogram, and having in the back of their minds the practical plan of first mastering that instrument under his guidance and then establishing electrocardiographic stations in our country, being not unmindful of the financial rewards which might follow such a course. If this impertinent view of the situation is the correct one, some of my countrymen were rudely shocked by arriving at Sir Thomas's laboratory with the expectation of studying the heart and finding that, Sir Thomas having lost all interest in that organ, they were put to work studying the blood vessels of the skin. But in any event, that important information about the peripheral vessels in both health and disease was emerging from Lewis's laboratory soon became known to me and doubtless to Brown also, because his book,[1] coming out about a year later than Lewis's,[2] is imbued with the physiologic viewpoint and is certainly among the first publications in the clinical field which reflected it.

The Cutaneous Histamine Reaction

My own first investigation in the peripheral vascular field was directly suggested by one of Lewis's experiments.[2] He had been interested in the reaction of the skin to histamine, then a new drug, which, when pricked into the normal skin, produced a reaction identical with the common mosquito bite; a reaction having most, but not all, of the attributes of the inflammatory reaction. Sir Thomas had found that if the circulation to an extremity was obstructed by an inflated blood pressure cuff, the reaction to histamine beyond the point of obstruction was markedly changed. In contrast to the normal, if the obstruction was slight the reaction developed more slowly; and if the obstruction was severe the reaction lacked both the central wheal and the wide area of erythema around it, the flare, the site of introduction of the drug being identified only by a small red spot of capillary dilatation.

These observations at once suggested to me that if the circulation was obstructed by disease the reaction would change similarly, an expectation easily proved to be the case.[3] So this reaction is a rough test of the effectiveness of the circulation in any diseased extremity, and, perhaps, by virtue of its close relation to the inflammatory reaction, a measure of the resistance of the part to infection and of the integrity of the local reflex mechanisms. When I followed 89 diabetic patients for five years the histamine reaction proved to be of prognostic value,[4] its abnormality indicating those more likely to get into trouble.

This histamine reaction, however, is only a rough measure of peripheral blood flow, for it is influenced by pressure as well as flow. Later work[5] clearly demonstrated that, when compared with the vasodilation test, the reduction of blood flow must be considerable before the histamine reaction changes markedly, but when flow is much reduced the change in the reaction can provide much useful information. In addition, not only does this reaction tell about blood flow but it also makes it possible to detect abnormality of the peripheral nerves, for the integrity of these nerves is essential to the development of the flare. Certain precautions have to be observed in making the test, but it works well on the warm wards with the patient in bed. The position of the extremities made a difference, the reaction appearing more promptly when the feet are dependent than when they are horizontal, and it appears still more slowly when they are elevated. The external temperature is also a factor, a cold room delaying the reaction, a warm one accelerating it. A normal person coming indoors after exposure to cold gives a delayed reaction for some minutes until he has warmed up. Areas of unusually thick skin must be avoided. So care must be given to the circumstances under which the test is made.

Nevertheless the test has the great advantage of complete simplicity, and it could be readily

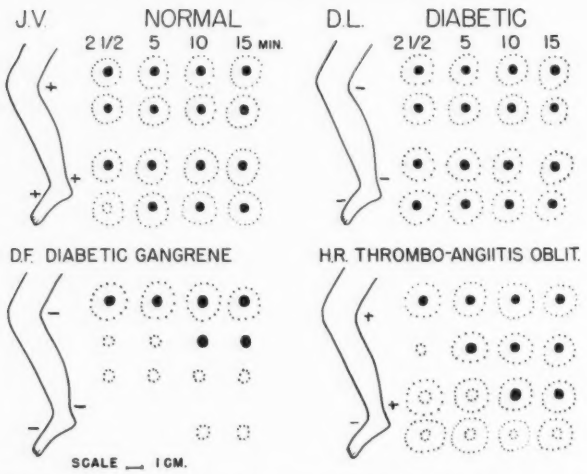

FIG. 1.* Histamine reactions at various positions on the thigh, leg and foot of one normal person and three patients.

The drawings of the histamine reactions are semidiagrammatic, as no attempt has been made to follow the exact outlines of the flare and wheal, which are likely to be rather irregular. The drawings of the reactions are in scale, not with the diagram of the leg shown nearby, but with the centimeter scale shown in the left lower corner. The solid black spot indicates a wheal; the dotted circle of approximately the same size indicates the red spot of capillary dilatation in the normal reaction which precedes the development of the wheal, and is replaced by it. The difference between these two was always decided by my ability to find the wheal by palpation with my eyes closed, since the wheal protruding above the surface is easily felt and the red spot cannot be felt. The larger dotted circle represents the flare. These reactions are placed at the level of the diagrammatic leg at which they were elicited in the patient, the uppermost being always above the knee, the lowermost on the dorsum of the foot. The two intermediate reactions were placed on the upper and lower leg, but not directly over the shin. The subject was lying on his back at rest.

Each reaction is represented by four diagrams which show its development in time up to 15 minutes. The plus and minus signs placed near the leg diagram indicate the presence or absence of arterial pulsation at corresponding positions in the subject.

J. V. was a healthy person with a normal blood pressure and the reactions are all normal, that is, they are completely developed within five minutes. Even in healthy persons there is a tendency for the reactions to develop more slowly in the more peripheral positions, and this can be seen at the two and one-half minute observation, in which the reaction on the dorsum of the foot has not as yet whealed.

D. L. was a moderately severe diabetic with a blood pressure of 130/80. Despite the fact that no pulsations could be felt in his leg beyond the femoral artery, the histamine reactions indicate an entirely normal circulation. Obviously an increased collateral circulation has completely compensated for the blocked main vessels.

D. F. was a diabetic with a blood pressure of 170/88 who had developed an area of gangrene between the fourth and fifth toes. Note the abnormality of the reactions obtained below the knee in contrast to the normal reactions persisting above it. There is no whealing of any reaction below midleg, while the whealing below the knee is retarded. No flares appear below the knee which indicates, when whealing is present, an abnormality of the peripheral nerves which is very common in diabetics. Also notice how far up the leg one must go before the reactions become normal.

H. R. was a patient with thromboangiitis obliterans with rest pain in his foot. Notice the persistence of the flares indicating that the nerves are normal, but there is no whealing on the dorsum of the foot, with some delay in the whealing above the ankle. Typically in thromboangiitis obliterans the histamine reactions remain normal much closer to the lesion than is the case in diabetes.

* Most of the data given in figures 1 and 2 have not been published previously. But some of the illustrations used have been redrawn from figures previously published in the *American Journal of Medical Science* and permission to use these data has been kindly granted by the editor and publishers of that journal.

performed by any doctor. One need only put a drop of 1:1000 histamine on the skin, prick the skin with a needle which passed through the drop—I used to prick through each drop seven times—and observe the time and character of the reaction which appears in the next few minutes. A series of such tests placed along the leg and on the foot is very informing. In healthy persons lying horizontal in a warm room, the distal reactions develop a little more slowly than the proximal, but they all become fully developed within five minutes, looking like a row of mosquito bites. In contrast, in peripheral vascular disease, although the tests placed above the knee develop normally those placed distally lag far behind and may never reach complete development during the 15 minute period of observation, lacking the central wheal, or the surrounding flare, or both. It is hard for me to think that the normality, or lack of normality, in this reaction does not disclose something well worth knowing about the condition, not only of the blood supply to the small vessels, but also of the small nerves which control them, surely factors of importance in any estimate of the ability of the part to respond effectively to stress, and I must admit some surprise that this simple physiologic test has not been more widely used by those interested in peripheral vascular disease. To try to revive your interest I have prepared some figures showing histamine reactions in patients with peripheral vascular disease (figs. 1 and 2).

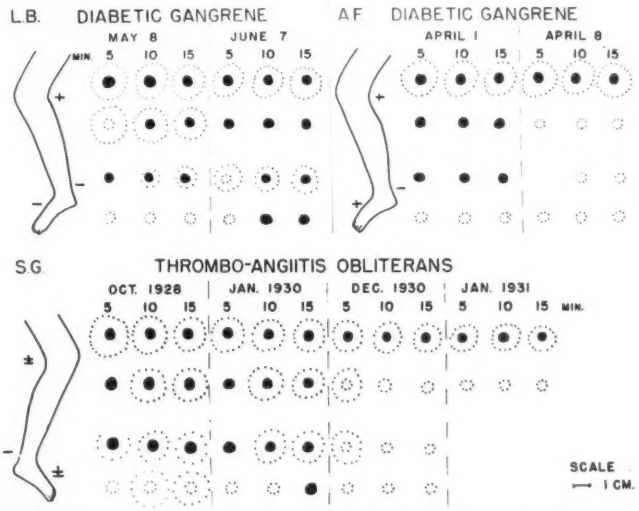

FIG. 2. Changes in histamine reactions with time. The symbols are the same as in figure 1.

L. B. had gangrene at the tips of the right first and third toes, which was treated conservatively and eventually healed. Note the improvements in the histamine reactions which indicate an improving collateral circulation. His blood pressure on May 8 was 140/70, on June 7 it was 148/70.

A. F. had a gangrenous area between the fourth and fifth toe. The clinical condition of the foot deteriorated rapidly and there must have been a marked obstruction of the circulation between the two tests as the degree of deterioration of the histamine reactions is most alarming. The blood pressure on April 1 was 142/70 mm. Hg; on April 8 it was 130/65. The patient came to amputation.

S. G. was followed for over two years. At first there was some improvement on conservative measures, but later there was marked progression and eventually the entire left great toe became gangrenous, and amputation was performed at midleg. The blood pressures for the four tests were 125/72, 132/68, 140/80, and 120/70.

PHYSIOLOGIC METHODS OF TREATMENT

Looking at peripheral vascular disease from the physiologic point of view, one sees the possibility of saving the limb threatened by arterial obstruction by paying attention to two matters: (1) by reducing as much as possible

the need for blood in the area supplied by the obstructed vessel, and (2) by increasing the supply of blood as much as possible by dilating the vessels still remaining open. And by such means one hopes to tide the patient over a period of acute ischemia until thrombi have been canalized and the development of collateral circulation has time to take place.

Needless to say, some of the methods advocated in 1928 are no longer in use today, but let us look over the list of therapeutic items advocated in Brown's book[1] (table 1) and select certain of them for further discussion of their physiologic implications.

Pumping Devices

An important therapeutic item on Brown's list is postural exercises. The rhythmic elevation and depression which constitute these exercises is presumed to increase the blood supply of the limb. Physiologically it is not only possible but probable that such exercises will increase the flow to any limb because of the changes in hydrostatic pressure on elevation and depression and the valves in the veins. But one wonders whether this pumping action is powerful enough to make the exercises worth while and whether the increase might not go to the working muscles where it is not needed rather than to the ischemic area which is so in need of it. Indeed studying the circulation of diseased legs by skin temperature measurements, I found it difficult or impossible to show that any increase in circulation to the skin resulted from such exercises. Certainly most of us nowadays believe that they are of minor importance. However, persons with peripheral vascular disease threatened with gangrene are likely to be in bed for a long time, and when I was treating such cases I used to think that exercises were psychologically useful in giving the patient something to do at regular intervals. Certainly the Saunders rocking bed would produce the same effect on the circulation and would have the great advantage of doing it constantly, even when the patient was asleep; and it pump without muscular exercise and so without diversion of blood to the muscles. Again one wonders whether the increased circulation and the gain to the patient are great enough to warrant the expense of the apparatus and its maintenance, but I can think of no other objection to the treatment, which probably has a small but real place in our armamentarium against obstructive vascular disease.

TABLE 1.—*Conservative Therapy of Thromboangiitis Obliterans 25 Years Ago (from Brown, Allen, and Mahorner, 1928)*

1. Prophylactic Care of Extremities
2. Smoking Discouraged
3. Warm Climate
4. Postural Exercises
5. Contrast Baths
6. Radiant Heat
7. Vasodilatation by Typhoid Vaccine
8. Removal of Foci of Infection
9. Sympathectomy

On the other hand the elaborate suction and pressure devices,[6, 7] reaching their highest degree of perfection in Landis' apparatus,[6] while they can be demonstrated to increase the circulation to a diseased limb somewhat, seem to have resulted in a gain hardly worth the effort and expense involved. In addition there was always the real danger that not only blood but also infection might be pumped through the tissues. But occasionally, especially after an acute embolus in an otherwise normal limb, the method seems to be of real help, color returning and pain diminishing. It takes skill to use such apparatus properly, and, turned over to unskilled technicians, the leg may be so constricted by the sealing cuff that more harm is done than good.

Heat and Cold

Two items on Brown's program, contrast baths and radiant heat, I wish to consider together, because increased knowledge of the physiologic mechanisms involved has resulted in the abandonment of these methods. I well recall my own initiation into the field. As a young visiting man at the University of Pennsylvania Hospital I found myself second in command of a ward full of diabetics who had come in large numbers to the hospital to receive insulin, which had just been discovered and so was available to us though it was not available

to doctors practicing outside large university centers. One of these diabetics came in with severe peripheral vascular disease, suffering from rest pain in one foot. I started to treat him as I had been taught to do, that is, I secured a foot cradle inside of which were a battery of electric lamps designed to play their radiant heat on the diseased foot. When I made rounds next day the patient said to me, "Doctor, my foot hurts more when it is in your cradle than if I keep it outside." In the height of my ignorance at the time, an ignorance that I believe was shared by the rest of the profession, I answered the patient this way: "The trouble is that the main blood vessels are plugged up and your foot is not getting enough blood. Heat is a very powerful dilator of vessels, the most powerful we know. Keep your foot inside the cradle and the heat will dilate the vessels and cause the foot to get more blood." The patient took my advice and kept his foot inside the cradle despite the increased discomfort; the foot soon went gangrenous and high amputation had to be performed.

One does not cause pain in patients lightly, and this most unfortunate episode started me wondering whether the patient had not known more about the situation than I did, and whether the gangrene would have ensued if he had not taken my advice and kept his foot in the cradle. I was so bothered about this that I started a series of experiments to answer the questions raised. I knew that the velocity of chemical reactions in vitro was increased as temperature rose. In one of my three summers at the Marine Biological Laboratory at Woods Hole I had attended the physiology course conducted chiefly on marine organisms, and there I had learned that in poikilothermic animals the rate of many vital processes is a function of temperature.[8] Also the basal metabolic rate of man increases roughly 7 per cent for every degree Fahrenheit rise in temperature.[9] Gessler[10] had found that raising the temperature of excised skin from 34 to 48 degrees increased its respiration by 30 to 100 per cent, heating above 48 degrees decreased oxygen utilization, above 52 degrees respiration ceased, probably due to death of tissue. And recently Horwitz and co-workers[11] showed that warming intact skin increases its oxygen tension until skin surface temperature reaches 40 to 45 C., then oxygen tension decreases. Normally the blood flow to a heated part is much increased, placed in hot water our hands become red and the pulse increases. In the sympathectomized paw of the dog Freeman and Zeller[12] found that blood flow varied directly with the temperature of the bath in which the paw was immersed. Perhaps therefore by heating the diseased part I had caused gangrene by increasing the demand for oxygen and other necessary materials brought by the blood, a demand met in the normal limb by a vasodilatation and an increased blood flow, which not only supplies more oxygen but also prevents undue rise of the temperature of the part by carrying heat away. But when my patient's diseased limb had been heated the demand for more oxygen that I had created could not be met because of the vascular obstruction which prevented the needed increase of blood flow.

I soon discovered many other cases in which gangrene had followed the application of heat. So it seemed of vital importance to study the effect of heat on limbs in which the main vessels were obstructed and to determine whether such treatment was beneficial or harmful. To answer this question I used a method which Sir Thomas Lewis had devised,[13] based on the estimation of the color of the skin by means of a color scale. My old friend, Dr. E. M. Landis, now professor of physiology at Harvard, had been working in Sir Thomas's laboratory and he had brought back a color scale made there; so I had an artist make several copies for me.

As you all know, in advanced peripheral vascular disease the skin changes color markedly but the abnormal color is by no means uniform throughout the involved area. To study the skin color of diseased limbs, and so determine the degree of cyanosis, one must therefore choose several areas each of which, marked with a spot of ink, can be matched with the colors on the scale in successive tests. The graduated colors on the scale—at one end the yellowish red of normal skin when the vessels are fully dilated and blood flow very rapid, at the other end the deep blue of full cyanosis—seldom

exactly matched the colors found on the skin of patients, but the method could be used none the less. One began the comparison by comparing the patient's skin color with that at the yellow-red end of the scale. If this scale color was plainly a yellower red than the skin of the patient, one then compared the succession of colors down the scale until it became doubtful whether a certain color was too yellow a red or not. One then moved to the bluer end of the scale, and finding this much too blue, one moved up the scale until one was doubtful whether the scale color was a bluer red than the skin. Thus it was usually found that a single scale color could be selected as a red neither too blue nor too yellow, and so the degree of cyanosis could be recorded, even though the color in the scale did not exactly match the color of the skin.

TABLE 2.—*Effect of Slowly Increasing the Temperature around the Foot of a Patient with Gangrene of the Great Toe*

Temp. (C.)	Color*		Sensation
	(1)	(2)	
25	XII	XIV	Severe Pain
27	XI	XIII	Still aching
29	VIII	IX	Pain now intermittent
30	VIII	X	Pain gone
32	VIII	X	Occasional twinge
33.5	VIII	X	Patient has gone to sleep
35	VIII	X	Awake—no pain
36	X	XI	Comfortable
37	X	XI	Comfortable
37.8	X	XI	Comfortable
38.6	X	XI	Continuous pain

* Colors recorded were observed (1) on the dorsum of the foot 2 cm. above the line of demarcation, and (2) 2 cm. above the second toe. On the Lewis scale the Roman numerals increase in size as the color becomes more cyanotic.

Such a color scale is extremely easy to use and in my opinion gives most valuable information. It has always seemed to me an excellent clinical instrument and I have never been able to understand why it seems to have dropped entirely out of use. Perhaps this is because there is no place where one can purchase these scales that I know of. But the advantage of having a rough quantitative measurement of the skin color of the diseased limbs is very great, as this color, so largely due to that of blood in the subpapillary venous plexus, reflects the oxygen content of the venous blood. Provided extreme cold is avoided, for cold makes the oxygen in blood less available to tissues, the degree of cyanosis of the skin is what one wants to know about peripheral vascular disease, because the oxygen remaining in venous blood measures the relation between the metabolic demands of that part and the oxygen supplied by the flowing blood, and so skin color is a physiologic measure of the patient's abnormality. To my mind the use of such a scale provides information bearing more directly on the point at issue than would the analysis of blood samples, taken from veins draining the diseased part. The difficulty with such samples, besides the practical point that the veins are usually constricted and it is hard to secure blood from them, is that the bulk of the blood drawn will come, not from the diseased areas where circulation is minimal, but from the most normal areas where circulation is relatively much better, so the result of chemical analysis may be misleading.

Provided with a color scale I was ready to perform a very simple experiment designed to answer my question of the effects of heating on a limb where vessels were obstructed. The discolored foot of a patient threatened with gangrene from peripheral vascular disease was placed in a tank of water and the temperature of the water was varied, while skin color was estimated by the scale at frequent intervals.[14] I also inquired from the patient concerning the presence or absence of pain, being particularly concerned with finding the temperature at which he was most comfortable. The results, an example is shown in table 2, were definite and clearcut. Most patients preferred a temperature of approximately 92 F. and at temperatures at or near this the skin color was best. In water hotter than this not only did pain begin but the foot often became bluer.[14] The temperatures colder than the optimum 92 F. also caused bluing of the foot, so that I thought of the temperature of 92 F. as the optimum for most persons, the point at which the blood supply most nearly met the metabolic requirements.

After these experiments the radiant heat cradle was discarded at the University Hospital and I believe that it is no longer used anywhere today. I built myself several types of thermo-regulated cradles[14] by which I could maintain any temperature I desired around the foot. In treating a diseased foot the cradle was started at a temperature of 92 F., but I always allowed the patients to change this to any temperature they found more comfortable. Most patients chose a temperature close to 90 F. which was in good accord with the results of my experiments. These thermoregulated cradles[15] had a vogue for a time but I believe they are used rather less today, probably because their maintenance and repair required more knowledge of electrical equipment than most doctors and nurses possess; and, in summertime, or indeed often in our usually overheated wards at other times of the year, the gain over an unheated cradle was perhaps not great enough to warrant the trouble of operation. But we have all learned a vitally important point, that one dare not apply anything but the mildest degrees of heat to an extremity to which the circulation is obstructed, for fear of producing an increased demand for blood which cannot be supplied, and for which destruction of the tissue may be the penalty. The proper therapeutic aim is to maintain the temperature of the foot at the level at which the relation of demand to blood supply is most favorable.

From this experience you will also see why I have been unsympathetic to the idea that diseased limbs should be artificially cooled. Certainly we hardly needed the modern experimental studies in frostbite,[16] such a problem in warfare, to tell us that cold would harm tissues. If there is any proper place for such measures at all, it would be when one had a gangrenous limb far beyond all aid except amputation, in a patient so ill that immediate amputation was contraindicated.[17] In such cases packing the diseased limb in ice might relieve pain and diminish the absorption of noxious products into the general circulation and so perhaps gain a little time in which the patient could be built up to undergo amputation with a better prospect of survival.

The Use of Vasodilating Drugs

The next proposal on Brown's therapeutic list is to dilate the vessels of the diseased limb by means of typhoid vaccine, and indeed by means of skin temperature measurements he proved that this could be accomplished. From our present vantage point of 25 years it is hard to realize the impact of this proposal, for the current medical view of the period was that the main vessels were altogether blocked and this view was supported by knowledge that the best vasodilators of the period, the nitrites, had been tried in peripheral vascular disease and found wanting, a fact which contributed to the pessimistic outlook of the time. The reason for this failure was borne in on me from some experience undergone several years after the publication of Brown's book.

The drug Mecholyl, having been synthethesized by Major, was being tested in Dr. Richard's laboratory of pharmacology, where I was working at the time, by the Belgian pharmacologist Simonart, and was proving to be the most powerful vasodilator known up to that time[18]; it would break through the action of adrenaline in animal experiments while the nitrites would not. I immediately seized upon the new drug in hopes that it would be of major assistance in peripheral vascular disease. I tried it both on healthy persons and patients in the clinic, seeking to record its vasodilating action by measuring the skin temperature of the feet.[19] Figure 3 shows such a record. The results not only disappointed me but they also greatly surprised me. After a subcutaneous injection of the drug violent effects appeared within a minute or two, the face flushed and became warmer as vasodilatation manifested itself there, but the feet became much colder. Obviously I was getting not a pure vasodilating action but a mixture of actions, vasodilatation in some places such as the face, but vasoconstriction in other places as in the feet where I so desired to secure the reverse. It was some time before the physiologic implications of this were clear to me, and before discussing this aspect of the situation in detail let us see what general principles can be learned from more recent experiments in the field.

Studies with the plethysmograph have thrown light on many aspects of this problem.[20] The physiologic phenomenon involved in getting an increased flow of blood to one part of the peripheral circulation has been intensively studied by Burch[21] and his associates[22] by means of plethysmographic technics over many years, and the experience has been summarized more recently. With their views of the matter I am

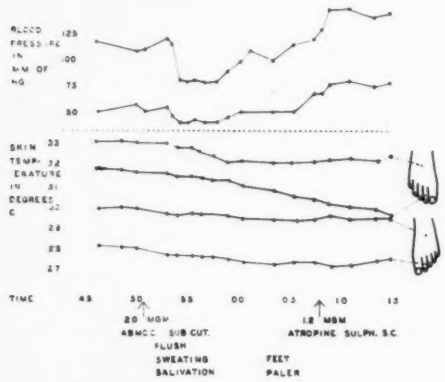

FIG. 3. The effect of a subcutaneous dose of 20 mg. of Mecholyl (acetyl-β-methylcholine chloride) to a patient with mild manifestations of peripheral vascular disease. Skin temperatures were taken with thermal junctions applied to both feet at the positions indicated. The patient's feet were exposed to a cool room. Time is given in minutes related to the hour.

Note that the sharp fall in blood pressure is accompanied by a continuous cooling of the skin temperature of the feet until the administration of atropine, which abolishes the Mecholyl action, reverses the trend in some but not all of the positions tested.

in entire accord; what one needs to remember may be briefly summarized as follows:

Blood flow to a foot may be enhanced by increasing the cardiac output but this also increases the blood flow to places where such increase serves no useful purpose. This is what happens when increased flow to a foot is secured by fever, as after typhoid vaccine, and by certain drugs. The injection of large amounts of salt solution intravenously[23] increases blood volume and must cause a vasodilatation somewhere in the body to accommodate it; thus the periphery may be included in a general vasodilatation, and if the injection is large enough some increase of cardiac output may be expected as well. But these methods should be thought of as a very inefficient way of increasing the blood supply to a foot. It would seem far preferable to increase the flow in the diseased foot by borrowing the blood from another part of the body which does not need it. Indeed as Burch and his collaborators[22] have shown by measurements made with several peripheral plethysmographs recording simultaneously, there is normally a continuous shifting of blood flow from one part of the body to another, a process which they dignify by the term hemometakinesia, and which they regard as serving the useful purpose of supplying the organs with blood according to their varying needs, with the greatest economy of effort. We still lack knowledge about shifts of blood flow between the peripheral organs in which it can be measured easily, and the abdominal organs in which, with the possible exception of the kidney, blood flow can be measured only with difficulty or not at all in man, but we have every reason to expect that an exchange of blood flow, a borrowing-lending process, similar to that demonstrated in man for two parts of the periphery, will also take place between the periphery and the deep organs, as many animal experiments indicate.

It is impossible to think of a generalized vasodilatation without a concomitant increase in blood volume and there is good reason to believe that rapid increments of blood volume are not possible to the body, as blood volume is restored so slowly after hemorrhage. Therefore the blood needed to fill vessels whose diameter has rapidly increased must be withdrawn from other vessels whose diameter must diminish correspondingly. A fall of blood pressure, as from a hemorrhage, causes reflex vasoconstriction. Therefore the train of events when one gives a powerful vasodilator like Mecholyl may be thought of as follows: vasodilatation of certain areas, fall in blood pressure, reflex vasoconstruction. So, far from having a pure vasodilator action we have a competition between dilatation and constriction. I do not know with certainty why dilatation always wins out in the face and constriction in the feet; perhaps the vessels of the "blush" area, more exposed to the elements than other parts of the body, might be thought of as more susceptible

to vasodilator influences than those vessels elsewhere in the body which are usually covered by clothing. Perhaps the constriction should be thought of as for the purpose of conserving body heat which is being lost from the dilated areas.[24] But whatever the reason, the fact remains that large doses of vasodilators by mouth or by injection are followed by constriction in the extremities, an effect the reverse of that sought in peripheral vascular disease. However, this line of thought gives us a hint; perhaps the way to get vasodilatation in the feet by means of drugs is to give them so that a fall in blood pressure is avoided as far as possible. This idea seems to be borne out by experience.[25] The slower acting choline derivatives such as Doryl[25] and Uricholine[26] have little effect on blood pressure; considerable increases of skin temperature of the feet may at times follow their administration, and I have occasionally seen very striking relief of rest pain, exceeding that secured by morphine, after the subcutaneous administration of these drugs, even though I was unable to detect a concomitant rise in skin temperature.[26] I presume such relief of pain was due to a vasodilatation too slight or too deep to be recorded by a skin temperature change.

Other factors than the state of cutaneous vessels enter into the problem of increasing the circulation to the feet, and one of these is the cardiac output, for you might well increase the flow to the feet by increasing flow to all parts of the body. The febrile reaction to the typhoid vaccine used by Brown would have just such an effect as is demonstrated in figure 4, in addition to effects on the peripheral vessels. But the peripheral effects of typhoid vaccine are mixed, an undesired vasoconstriction in the stage of the chill while body temperature is rising, then the desired vasodilatation as the chilly sensations pass off and are succeeded by the feeling of warmth. So this method of securing vasodilatation in peripheral vascular disease is far from ideal, for vasoconstriction has an element of danger in this disease; thrombosis sometimes follows it. In addition treatment with typhoid vaccine could not be indefinitely repeated because the development of immunity soon abolished the febrile response, and it is little used today.

We are searching even now for the perfect means of increasing the flow of blood through the feet, and looking for the perfect drug which will cause vasodilatation without stimulating cardiac output, and so will increase the flow to the diseased extremity by diversion of blood flow from other sources. The direct introduction of drugs into the skin of the diseased extremity by iontophoresis[27] obviously meets this need, but the special skill and apparatus required have limited the usefulness of the method. Injections of vasodilators directly into

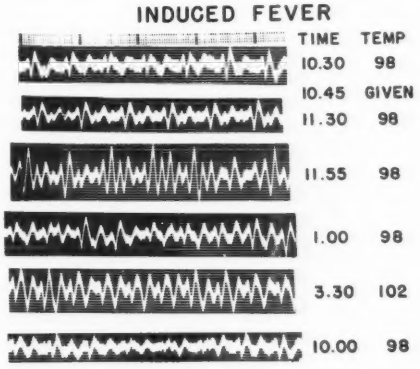

FIG. 4. Ballistocardiograms showing the effect of typhoid vaccine given to a case of peripheral vascular disease. The points of interest are the increase in ballistic amplitude which occurs before the rise in temperature, the tachycardia and diminution of amplitude at the time of the chill, the continuing tachycardia and increased amplitude when the fever rose, and the final return to an amplitude somewhat smaller than the control. The reproduced tracings are one-third actual size. The time record at the top applies to all the ballistocardiograms; its longest interval is one second.

Typhoid vaccine was given at 10:45 a.m. The calculated cardiac output at 11:30 a.m. does not differ from the control. By 11:55 a.m. the patient had a sensation of fullness in the head though his temperature had not yet risen. At this time the cardiac output had increased by 61 per cent of the control value. At 1 p.m., at the time of the chill, it was 32 per cent above the control value, and at 3:30 p.m., the temperature having risen, it was 65 per cent above the control value. By 10:00 a.m. next day the febrile reaction had passed off and the calculated cardiac output was 9 per cent below the control value of the day before.

the artery supplying the part has been tried recently.[28] Such drugs might be injected through one of the small plastic catheters[29] which can be inserted into an artery through a needle and left in situ without discomfort after the needle is withdrawn. This seems well worth trying as an emergency procedure, though how long this could be properly continued has not been determined, and such procedures are still in the experimental stage.

Our chairman, Dr. Montgomery, with Dr. Horwitz and their collaborators[30] have been among the most active in the attempt to identify a satisfactory peripheral vasodilator which can be taken by mouth or injection. It was first found that our old friend alcohol met the need for a gentle vasodilator, which would increase the circulation to the feet without stimulating the cardiac output or reducing the blood pressure, better than the other drugs available at that time.[30] Recently Priscoline has looked more promising.[31-36] Whether the newer drugs on the list, especially the adrenolitic group and the sympathetic blocking agents,[36, 37] will be found superior to these older drugs I do not know, but I do know that our methods of testing for effects of these drugs have greatly improved, and that by taking skin temperatures in a thermoregulated cool room, with a ballistocardiogram to detect effects on cardiac function, an evaluation of the steady stream of new drugs is possible with an accuracy not available a few years ago. And that there is a place for drug therapy in peripheral vascular disease is obvious.

Harmful Vasoconstriction

The same tests used to identify beneficial drugs may also be applied to learn about agents harmful to the patient and certainly the discovery of the constrictor effect of the nicotine in smoking tobacco and subsequent realization of its harmful effects in peripheral vascular disease have permitted a great advance in therapy. There seems no doubt that, as originally pointed out by Silbert,[38] these patients should avoid the use of tobacco; Brown realized this in 1928, and Grace Roth has contributed much to our knowledge of the subject more recently.[39] There is no longer room for doubt that the improvement following abstinence from tobacco may be long continued.[40]

Reflex and Postprandial Vasodilatation

I must not pass the subject of vasomotor responses in peripheral vascular disease without emphasizing another most effective means of securing vasodilatation in the extremities. We dare not heat the diseased limb itself, but we can readily secure a powerful vasodilator effect on the vessels of the diseased limb by heating some other part of the body like the hands or abdomen, as was shown by Lewis in work summarized in his later book, "Vascular Disorders of the Limbs,"[41] and by Gibbon and Landis.[42] Here is a maximal vasodilatation secured without any of the untoward side effects so often found after drugs, and it seems the ideal method of securing vasodilatation for short periods of time in bed patients. But prolonged heating is not well tolerated even by bed patients, and heat to the body cannot be readily applied to ambulatory patients. We can, however, keep all our patients warm, and I do not doubt that this is an important factor in keeping their peripheral vessels dilated, as Brown well knew.

Vasodilatation of fingers and toes also follows the ingestion of a substantial meal by normal subjects and the duration of the vasodilatation can be prolonged by feeding at frequent intervals.[43] I am not aware of data indicating that similar effects can be secured in peripheral vascular disease but one expects that they could.

Surgical Vasodilatation

It is the difficulty of securing long-enduring vasodilator action in a diseased limb by means of drugs or physical agents which makes the surgical means of securing it so attractive, and Brown's series, operated upon by Adson,[44] was one of the first, if not the first, in which advantage was taken of the new knowledge concerning the effects of sympathectomy on peripheral vessels. This operation brings about a long continuing increase in blood flow to the denervated part as Brown showed,[1] and this has been amply confirmed everywhere.[45] This operation has since been used all over the world, with marked benefit in many cases.

That it is no final answer all would agree today, I believe. Perhaps the fault lies in the increased sensitivity to adrenaline which occurs in vessels deprived of their sympathetic innervation though this effect is easier to demonstrate in animal experiments than in man. Perhaps, as Freeman[46] has emphasized, the ability to dilate the vessels preferentially may be lost within the denervated area, so that despite the increase of blood flow to the limb as a whole, the ability to concentrate a greatly increased blood flow around an area of local infection may be impaired by the denervation. Perhaps the disease progresses or the nerves regenerate, or both, but in any event the beneficial effect of sympathectomy is usually limited to a period of years. You are as familiar with the evidence as I, and I do not see the need of reviewing it here.

In addition, rapid deterioration of a diseased extremity after sympathectomy is seen occasionally, and this aspect has been recently emphasized[47] with the thought that somehow the denervation was allowing the extra blood to flow through A-V anastamoses without increasing the flow at the point of need, or was adversely affecting the collateral circulation. Certainly our lack of knowledge of the physiology controlling the distribution of blood within a single part, and of the factors which aid or hinder the development of collateral circulation is greatly to be deplored—it is a point on which the histamine reaction would throw light—for while our therapeutic methods may tide the limb over acute episodes, we count on the development of collateral circulation to restore the limb to health; and increased knowledge of the factors which assist, and of those which hinder this development is greatly needed.

Certainly the other operative procedures have not fared as well as sympathectomy. Caudal block with procain, producing the same vasodilator effect, but for a period of hours only, has a place; but the operation of sectioning the peripheral nerves, though it temporarily relieved pain by rendering the part anesthetic, has proved to have so many untoward aftereffects that it has been abandoned in most clinics.

Early Adventures with Oxygen and Desiccation

Before going on I shall yield to the temptation of reminiscing about some of my early adventures with a type of therapy which taught me a great deal though the method itself has long since been properly discarded. That oxygen could penetrate the skin had long been known to physiologists, and, with oxygen tents for pneumonia all about my ward I began to wonder what would happen if a cyanotic foot was placed in such a tent. I tried and the answer was that nothing happened that I could see.[14] But in such a tent the concentration of oxygen could not be raised above 50 per cent so I arranged a bell jar to hold a foot exposed to much higher concentrations, and I still recall my excitement when, on exposing a deeply cyanotic foot to nearly 80 per cent oxygen I saw it turn a vivid scarlet, about the color of a boiled lobster, and this striking change was accompanied by relief of pain.[14] One of these old experiments is recapitulated in table 3. Greatly encouraged I arranged a foot cradle covered by rubber sheeting which would permit the exposure of the feet to high concentrations of oxygen while the patient was in bed and soon after an ideal opportunity presented itself which enabled me to try my new therapy. A young woman with severe rheumatic heart dis-

TABLE 3.—*Effect of Increasing Concentration of Oxygen around the Foot of a Patient with Gangrene of the Great Toe*

Time	Oxygen	Color*		Sensation
		(1)	(2)	
	(%)			
12:25	21	XV	XIII	Severe pain
12:30	50	XV	XIII	Severe pain
12:35	68	XIII	XII	Pain better
12:50	77	XII	XI	Pain gone
1:10	82	VIII	XI	Comfortable
1:40	84	VII	X	Patient asleep
3:45	74	VI	X	Comfortable
3:53	21	VI	XII	Pain begins
4:00	21	IX	XII	Pain persists

* The colors were read at (1) 2 cm. above the line of demarcation at the base of the great toe, and (2) on the dorsum of the proximal phalanx of the second toe. On the Lewis scale, the Roman numerals increase in size as the color becomes more cyanotic.

ease,[14] wide open aortic regurgitation and auricular fibrillation, six weeks after cesarian section suffered from embolism first in one leg and three days later in the other. On admission both feet were cold and edematous, with mottled cyanosis below midleg. Because of the severe cardiac complications the surgical consultant, a man extremely sensitive about his operative mortality, believed the patient would not survive two amputations and firmly declined to interfere. Now this was the same surgeon who had advised bilateral amputation in my case which recovered without it, so perhaps he winked the other eye when he left me with the responsibility. I had no choice but to go ahead and do the best I could. At that time my apparatus would permit the treatment of only one leg at a time with oxygen, so the right, the worse leg, was inserted in a thermo-regulated cradle with a gas tight cover and kept exposed to a concentration of 60 per cent to 80 per cent oxygen as determined by frequent analyses. This had a most striking effect on the color of the skin of this leg; cyanosis disappeared, many areas turned bright red and pain in it diminished, in contrast to the other leg which, exposed to room air, remained both painful and cyanotic. The accumulation of moisture within the cradle covered with air-tight material caused trouble, but I soon learned to prevent this by desiccation of the contained air by pans of calcium chloride placed within the cover. However, despite the encouraging change of color of the right, gangrene started in the toes of both legs.

Within a few days my apparatus had been altered to permit both legs to be exposed to the high concentration of oxygen and the improvement in color of the left leg then equalled that of the right. Nevertheless, gangrene slowly ascended both legs at an equal rate, apparently uninfluenced by the treatment employed. Doubtless the oxygen did not penetrate deeply into the tissues, but I prefer another explanation for my failure, for I slowly came to realize how much needed material the blood carries to the tissues besides oxygen. By putting oxygen through the skin we could restore its oxygen tension to normal, but the tissue died nonetheless. So while it is now possible to measure oxygen tension in the skin by polarographic methods with rough accuracy as Dr. Montgomery and Dr. Horwitz have done,[48] and to raise the oxygen tension both deeply and superficially in the extremities by having the subject breathe pure oxygen,[49] as they have shown, I have little hope that much of great practical therapeutic value can be secured by such methods.

But another part of that experience may still be of some interest to those who are interested in the therapy of peripheral vascular disease. The desiccation I used to keep down the moisture content of my closed gas chamber around the legs had a most interesting effect.[14] My desiccators collected about 50 cc. of water a day and the gangrenous areas became mummified, shrunken to about half the natural size of the part and with a surface as hard as wood. The desiccation kept down all infection until, a line of demarcation forming just below both knees, spontaneous amputation began. This cleavage finally went down to the bones which were eventually cut through by the surgeon without anesthesia and without pain, leaving the ends of the bones protruding from the stumps, which were cleaned up by maggots, a treatment then in vogue. The patient stood this well, the stumps became clean and were granulating nicely, and I was envisioning the ease of attaching artificial limbs to the projecting bones. But she died of heart failure three months and six days after her admission and about three weeks after the surgical completion of the spontaneous amputation.

Modern surgical technics and the antibiotics have made this experience sound medieval, and it was indeed a dreadful ordeal for the most unfortunate patient, something to be avoided at all cost, but I have often wondered whether desiccation might not have a small place somewhere. The old conceptions were of the most dangerous "wet" gangrene, and the far less dangerous "dry" gangrene, and it is certainly in our power to convert the former to the latter by means of desiccation. This experience occurred long before the discovery of the antibiotics and had we been provided with these modern therapeutic agents we might have done much better for the unfortunate patient, as it

was infection in the line of demarcation which was our chief difficulty. I am glad to see that interest in conservative measures for the treatment of gangrene has not entirely died, there is a brief article on this field in a recent number of the *Journal of the American Medical Association*.[50] Let us not forget the healthy tissue sacrificed because the surgeon must amputate so far above the level of the lesion. Perhaps with thought, skill and inspiration we could do better for these unfortunate patients than we do now.

Newer Methods of Treatment and Prevention

For the sake of completeness let us now consider some of the newer methods which have been of no little service, although, before discussing them, I will have to admit that my own experience with them has been slight; for by the time they appeared on the horizon I was turning my attention to other matters.

The idea that thrombosis was the final event in the train which closed the vessel is an old one and the attack by anticoagulants a logical one as soon as drugs of this nature became available.[51] Here I must pause, however, to mention an experience which has had considerable effect on my view of the matter.

A most emaciated young woman with rheumatic heart disease and wide open aortic regurgitation was admitted to my ward many years ago. Because of the combination of emaciation and aortic regurgitation the pulsation in her peripheral arteries was visible, and of course palpable also, to a most unusual degree; it could be seen all the way from the axillas to the wrists. While under my care the patient had a sudden pain in the right arm and it was found that the pulsation had disappeared below mid arm. Indeed the point of obstruction, surely embolic, could be located exactly, for pulsation in the brachial artery was seen down to a definite point, and there it stopped. We had no anticoagulants in those early days so we simply watched the arm closely, and I was greatly surprised to see how rapidly the circulation was restored. The lower limit of visible pulsation moved slowly down the arm and within 48 hours no sign of obstruction remained. Certainly I had been underestimating the ability of the body to dispose of an intravascular obstruction which, in this case, was probably an embolus of clotted blood, with thrombosis below it. Certainly we have the right to attempt to assist the natural process of restoration by using anticoagulants, even though strong positive evidence of their effectiveness is hard to secure in any given case, and the published studies deal chiefly with their effect in heart disease, rather than peripheral vascular disease.

I have no need to emphasize the tremendous contribution of the antibiotics to the therapy of peripheral vascular disease. In the old days it was so often infection which led to the change from the chronic disease to the acute emergency, and with these new agents at hand the outlook for the infected case has changed greatly for the better. In the old days the patient's attempts at local antisepsis sometimes led to trouble, and the use of tincture of iodine as a routine antiseptic was one of the most frequent causes of disaster to cases of peripheral vascular disease in my early experience. That highly irritating and painful agent, originally designed as a stock solution for dilution before use—it is the only official iodine solution that can be diluted with water in all proportions without precipitation—by some trick of fate became the household antiseptic of choice of thousands of American homes, and I fear was prescribed by a host of doctors and even more nurses, perhaps with the thought that the severe pain caused by its application to a wound was somehow a testimony to the power of its beneficial action. We now think of this same pain as providing strong evidence of its destructive action on living tissue. Tincture of iodine is gone for good, I think, rated as causing so much tissue destruction that liability to infection was increased by the presence of devitalized tissue, a factor which might overbalance the drug's undoubted killing action on bacteria. But so popular was it that I well recall my struggles to get it out of the medicine chest in my own home. Indeed it took a second world war to get tincture of iodine out of the first-aid kit and directions of no less an organization than the American Red Cross. But it has gone for good now, and there will be fewer cases of

gangrene among those with peripheral vascular disease in consequence.

I must also say a word about more positive preventive measures which are now taught to those with diminished circulation to the feet, and so living under the constant threat of trouble. Patients are nowadays educated on such hygienic measures as extreme cleanliness in the care of the skin, keeping the feet warm and dry, wearing thick stockings and well fitting shoes, avoiding all trauma, especially when cutting the nails, avoiding the application of chemical irritants, and especially to seek medical advice immediately for the smallest trauma or infection. It is hard to get positive data on the effectiveness of any preventive program, but I have little doubt that such educational measures are a major factor in the improvement of the general outlook for peripheral vascular disease, which has been so noteworthy in my medical lifetime. In the school year before Brown's book was published, 1926 to 1927, the total number of major amputations of the leg done on the general surgical service of the University of Pennsylvania Hospital was 24, 25 years later the number of major amputations of the leg in the same period of time had diminished to 13, although in this interval the clinic, judged by the total number of major operations done, had increased over two-fold. So I conclude that preventive measures and conservative treatment are saving about three-fourths of the cases who formerly came to major amputation.

I must end by saying that I do not take a hopeless view of the possibility of a direct attack on arteriosclerosis itself. Starting my medical career before the first big break, insulin, I have seen the medical wards change completely during my medical lifetime, and certainly the advance of medical knowledge at this moment is as rapid as at any time in history. Animal experiments have demonstrated that lesions much like, or as some claim, altogether similar to human atherosclerosis can be produced, and after establishment will retrogress under appropriate conditions.[52] And I have been extremely interested in some experiments being conducted by Dr. Urbach of my medical school and my former associate, Dr. Hildreth,[53] on a group well known to be subject to early atherosclerosis, the idiopathic hypercholesterolemics. Placed on an extremely low fat diet for a long period of time the visible skin lesions of several of these patients have regressed and disappeared. Whether the invisible arterial lesions do likewise I do not know, but Dr. Montgomery tells me he has seen peripheral pulses in the limb of one of these cases absent at the beginning of the diet return after the patient was so treated for about six mouths, which Dr. Urbach tells me is not a unique experience. This is far from conclusive evidence, but it is ample reason for continuing attempts in this direction.

So I come to the end of my lecture. An old teacher from whom I learned a great deal, Professor E. G. Conklin of Princeton used to say, "Things are not discovered, they grow." This is particularly true of the peripheral vascular field which has seen, not epoch making discoveries, but steady growth, until the outlook for those with the misfortune to suffer from obstruction of the peripheral circulation is far different from what it was 25 years ago. And in this growth George Brown played a worthy part.

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* No attempt has been made to give a complete bibliography of the wide range of subjects covered in this lecture. The references given are to older work which seems to the author unusually important and to very recent work which contains references to other papers in the field. By looking up the bibliographies of these recent papers the author believes that a complete coverage of the field could be secured by anyone who was interested.

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Role of the Liver in Excretion and Destruction of Digitoxin

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The role of the liver in the excretion and destruction of digitoxin was studied in the rat, rabbit, dog and man (in part). It was found that no more than 10 per cent of a given dose of digitoxin is excreted in the bile of the animals tested and none could be detected in the bile of two human subjects. Evidence was obtained which suggested that in the rat and rabbit, the liver was able to destroy a large amount of injected digitoxin.

IT HAS generally been assumed that because the liver excretes the major portion of administered ouabain or strophanthin[1-3] it probably excretes digitoxin in the same manner. However, Hatcher and Eggleston[1] have been the only investigators who have attempted to study the hepatic handling of digitoxin and their results were inconclusive because of the relative inadequacy of their assay method. Thus, exact quantitative knowledge of the role of the liver in the excretion or destruction of digitoxin in the animal body is completely lacking.

The embryonic duck heart preparation, however, has allowed the microassay of digitoxin in various biologic tissue and fluids[4,5] including the liver. We have been able in the present study to assay digitoxin, when present, in the bile of various animals. It has been possible therefore by (1) analyses of bile as well as by (2) analyses of blood and tissues, before and after (a) bile ligation, and (b) partial hepatectomy, to determine the probable role of the liver in the elimination or destruction of digitoxin in various animals including man. The present report contains these results.

METHODS

A. Physiologic Procedures

Bile was collected from the unanesthetized rat and rabbit by a method previously described.[6] Care was taken to collect bile from the common duct of the rabbit proximal to the cystic duct. Bile was collected from the unanesthetized dog by means of a T-tube type of cannula previously inserted into the common duct.

Partial hepatectomy was performed in all species by surgical removal of 55 to 76 per cent of the liver. The excision was performed by application of a ligature to the base of each lobe to be removed, followed by excision of the lobe. Care was taken to insure the continued biliary excretion of the hepatic remnant left behind. Digitoxin was injected intravenously immediately after hepatectomy had been performed.

B. Assay of Digitoxin in Various Biologic Media

The bile content of digitoxin was assayed in the following manner. One cc. quantities of bile to which 1, 2, 4, 6, 8, 10, and 12 microgram quantities of digitoxin respectively had been added were extracted with 20 cc. of absolute alcohol by shaking for one hour. They were filtered and the filtrate evaporated to dryness at 70 C. in vacuo. The residue was taken up in 5 cc. chloroform, concentrated to one-third volume, stored at 20 C. for one-half hour, and then the supernatant fluid was decanted. It was evaporated to dryness and taken up in 20 cc. of Tyrode's solution by shaking for one hour. The average time taken for the occurrence of the "digitalis effect"[4] was observed for each sample. In this manner, standards were established by which a bile sample containing as little as 1.0 microgram of digitoxin per cubic centimeter of bile could be assayed.

The digitoxin content of tissues and serum were assayed according to methods previously described.[5]

RESULTS

A. The Hepatic Excretion of Digitoxin

1) *In the Rat.* A small but significant fraction of digitoxin is excreted in the bile of the rat. After an average intravenous injection of 312 micrograms of digitoxin into a rat, the bile collected during the first 24 hours (see table 1)

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contains 32 micrograms or about 10 per cent of the administered dose. None could be detected in the bile excreted the second day.

The above discovery of the relatively small amount of digitoxin excreted by the liver of the rat was confirmed in several different experimental studies. First, the digitoxin content of the serum of 24 rats that had been subjected to biliary obstruction was compared with that of a similar number of normal rats, 6 and 24 hours after the intravenous injection of 1.0 microgram of digitoxin per gram of body weight. After six hours the average content of digitoxin was 0.6 and 0.4 microgram per cubic centimeter of serum in the ligated and normal rats respectively. At the end of 24 hours, no digitoxin was found in the serum of either group. These observations, therefore, indicated that biliary obstruction, per se, resulted at best in only a slight retardation in the rate of disappearance of digitoxin from the blood, and probably the body also, of the rat.

The relatively small role of the biliary tract in the *excretion* of digitoxin was suggested also by the relatively small increase in the urinary excretion of digitoxin observed in rats, after biliary ligation. The average urine of eight ligated rats contained 11 micrograms (range: 8 to 14 micrograms) and that of normal rats, 6 micrograms (range: 4 to 10 micrograms) during the first 24 hours after injection of digitoxin. These results also show that the relatively unchanged rate of disappearance of digitoxin from the blood after biliary ligation, noted above, was not due to the substitution of renal for hepatic excretion of digitoxin.

2) *In the Rabbit and Dog.* Digitoxin was found in the bile of both the rabbit and dog. The bile from four rabbits during the first hour after intravenous injection of digitoxin (0.5 microgram per gram of body weight) was found to contain approximately 3 micrograms per cubic centimeter or an average total of 25 micrograms (see table 1).

The biliary excretion of digitoxin in the rabbit was studied in a second manner. A previous study[7] had demonstrated that injected digitoxin rapidly disappeared from the heart, lung, and liver of the rabbit after administration of the drug. Therefore, these organs in both normal rabbits and those subjected to biliary ligation were analyzed for their digitoxin content one hour after its intravenous injection (0.5 microgram per gram of body weight). If biliary excretion were responsible for the observed disappearance of digitoxin from tissue, then the tissue content of digitoxin in the ligated rabbits would have been higher than that of the controls. Such was not found to be the case. The average digitoxin content of the heart, lung, and liver was 0.3, 0.5, and 0.6 microgram per gram of wet tissue respectively in the control group of six rabbits, and 0.40, 0.5, and 0.5 microgram per gram of tissue in the group of five ligated rabbits. It appeared then that the rabbit was similar to the rat in its biliary handling of digitoxin.

Biliary excretion in the dog appeared to be similar to that observed in the other two species. The average biliary excretion of digitoxin by two dogs for the first 24 hours after the intravenous injection of approximately 1375 micrograms (0.1 microgram per gram) was 163 micrograms or about 12 per cent of the administered dose.

3) *In Man.* Bile was obtained from two different individuals who had had biliary fistulas following gall bladder surgery. Liver function of both patients was normal. Preliminary assay indicated that if 0.5 microgram of digitoxin was added to 1.0 cc. of this bile, it could be detected. Each of the patients was given 1.2 mg. of digitoxin by vein, and then the bile was collected daily for three days and assayed. The first patient, a man of 68 years, drained 160 and 375 cc. of bile respectively the first and second days. The second patient, a man of 50 years, drained 89 and 114 cc. respectively the first and second days. No digitoxin could be detected in any of the four samples of the two individuals.

These negative findings, of course, do not indicate that the human liver excretes no digitoxin. They do suggest, however, that bile contains less than 0.5 microgram of digitoxin per cubic centimeter after injection of 1200 micrograms of the drug. Since the average person excretes approximately 500 cc. of bile per day,[8] this suggests that an amount of digotoxin less than 250 micrograms of the 1200 micrograms

given is the maximal quantity capable of being excreted in bile.

in the rate of disappearance of digitoxin from both its tissues and blood. Thus (see table 2),

TABLE 1.—*Digitoxin Content of Bile after Injection of Digitoxin*

Rat Bile

Rat	Amount Digitoxin Injected (μg.)	Bile (0-24 Hours)				Bile (24–48 Hours)		
		Volume (cc.)	Digitoxin Concentration (μg./cc.)	Total Digitoxin (μg./24 hrs.)	Per Cent Excreted (24 hrs.)	Volume (cc.)	Digitoxin Concentration (μg./cc.)	Total Digitoxin (μg./24 hrs.)
0	290	7.5	4	30	10			
41	312	11.0	2	22	7			
78	224	9.5	4	38	17			
79	360	15.5	2	31	9			
90a	365	17.0	2	35	10	14	N.D.*	N.D.
91	333	17.5	2	35	11	13	N.D.	N.D.
99	300	—	—	—		14	N.D.	N.D.
Average....	312	13.0	3	32	10			

Rabbit Bile

Rabbit	Amount Digitoxin Injected (μg.)	Bile (0-60 Minutes)			
		Volume (cc.)	Digitoxin Concentration (μg./cc.)	Total Digitoxin (μg./1 hr.)	Per cent Excreted (1 hr.)
1	1596	11.0	3	33	2
2	1362	6.5	3	20	1
3	1471	11.0	3	33	2
4	1053	5.0	3	15	1
Average.....	1371	8.4	3	25	2

Dog Bile

Dog	Amount Digitoxin Injected (μg.)	Bile (0–24 hours)			
		Volume (cc.)	Digitoxin Concentration (μg./cc.)	Total Digitoxin (μg./24 hrs.)	Per Cent Excreted (24 hrs.)
1	1250	128	1	128	10
2	1500	198	1	198	13
Average.....	1375	163	1	163	12

Human Bile

Case	Amount Digitoxin Injected (μg.)	Bile (0–24 Hours)				Bile (24–48 Hours)		
		Volume (cc.)	Digitoxin Concentration (μg.)	Total Digitoxin (μg./24 hrs.)	Per Cent Excreted (24 hrs.)	Volume (cc.)	Digitoxin Concentration (μg./cc.)	Total Digitoxin (μg./24 hrs.)
1. A. S.	1200	160	N.D.	N.D.	—	375	N.D.	N.D.
2. A. A.	1200	89	N.D.	N.D.	—	114	N.D.	N.D.

* None detectable.

3. *The Hepatic Destruction of Digitoxin*

1) *In the Rat.* Removal of 66 per cent of the liver of a rat leads to a marked reduction

unlike the normal rat and the rat with simple biliary obstruction, the partially hepatectomized rat has considerable digitoxin in his serum

(0.4 microgram per cubic centimeter) 24 hours after injection of the drug. Moreover, although there was no detectable digitoxin in the heart, lung, or liver of the normal rat at this time, the heart, lung, and liver of the partially hepatectomized rat contained 0.30, 0.10, and 1.30 microgams of digitoxin per gram of tissue respectively. These results indicated that the liver either absorbed or destroyed a considerable fraction of the digitoxin given to the rat.

2) *In the Rabbit and Dog.* Drastic subtotal hepatectomy interfered moderately but not profoundly (see table 2) with the rate of disappearance of digitoxin from the tissue of the rabbit. The heart, lung, and liver tissues of six normal rabbits contained an average of 0.3, 0.5, and 0.6 microgram of digitoxin per gram respectively, one hour after intravenous injection of the drug (0.5 microgram per gram of body weight). Similar tissues of five rabbits subjected to partial hepatectomy contained an average of 0.6, 1.10, and 0.9 microgram of digitoxin per gram respectively. In other words, hepatectomy of this degree led to a retention of about twice as much digitoxin in the tissues, one hour after injection of the drug. Here again, the results are in contrast with those following biliary obstruction alone.

Partial hepatectomy of three dogs (see table 2) did not appear to influence the rate of disappearance of digitoxin from the representative tissues studied.

TABLE 2.—*The Effect of Partial Hepatectomy on Rate of Disappearance of Digitoxin from Animal Tissues*

Intact Animals (Control)					Partially Hepatectomized Animals					
No. of Animals	Digitoxin in Tissues (μg./Gm.)				No. of Animals	Hepatectomy (Per cent)	Digitoxin in Tissues (μg./Gm.)			
	Heart	Lung	Liver	Serum			Heart	Lung	Liver	Serum
					(*A. Rat*)†					
8	N.D.*	N.D.	N.D.	N.D.	16	66	0.3	0.10	1.3	0.40
Range	—	—	—	—	—	(60–74)	(0.05–1.0)	(0.0–0.5)	(0.05–4.0)	(0.2–0.9)
S. E. Mean	—	—	—	—	—	—	±0.05	±0.04	±0.32	±0.07
					(*B. Rabbit*)‡					
6	0.3	0.5	0.6	—	5	74	0.6	1.10	0.9	—
Range	(0.2–0.5)	(0.1–1.0)	(0.4–0.6)	—	—	(72–76)	(0.5–0.7)	(0.5–2.0)	(0.5–1.3)	—
					(*C. Dog*)§					
3	0.3	0.1	0.1	—	2	53	0.3	0.1	0.1	—
Range	(0.2–0.4)	(0.1–0.2)	(0.1–0.2)	—	—	(50–56)	(0.3–0.3)	(0.1–0.1)	(0.1–0.1)	—

* No Digitoxin detectable (less than 0.05 micrograms per gram).

† Each rat was given 1 microgram of digitoxin per gram of body weight and the tissues were obtained and analyzed 24 hours later.

‡ Each rabbit was given 0.5 microgram of digitoxin per gram of body weight and the tissues were obtained and analyzed one hour later.

§ Each dog was given 0.2 microgram of digitoxin per gram of body weight and the tissues were obtained and analyzed one hour later.

Discussion

The present studies indicate that the liver of various laboratory animals is able to excrete about 10 per cent of a given dose of digitoxin during the first 24 hours after its administration. No biliary excretion of digitoxin, however, was observed in any animal 24 hours after injection. These observations indicate that the major pathway for the disappearance of digitoxin in the animal is not by hepatic excretion of the *intact, unchanged* glycoside, or aglycone.

Our inability to detect digitoxin in the bile of either of two patients only allows us to postulate that the human subject cannot excrete more than 20 per cent of a given dose. He possibly excretes much less or none.

These results, of course, suggest that biliary

excretion is not the major pathway for the elimination of digitoxin from the blood and tissues of either animal or man. On the other hand, the liver of the rat, and probably of the rabbit too, appears to have some method of ridding the body of this drug. This was shown by the marked change in the rate of disappearance of digitoxin effected by partial hepatectomy. It would appear that this hepatic process is one of destruction or alteration of the drug. Thus, it was found in a previous study[7] that although rat liver rapidly took up, and stored digitoxin after its intravenous administration, the drug nevertheless could not be found in this organ 24 hours after its injection Since this disappearance could not be accounted for by escape to some other tissue,[7] by renal excretion,[9] by intestinal excretion,[10] or as shown in the present study, by biliary excretion, the conclusion appeared inescapable that a destruction or drastic alteration of the digitoxin had occurred in the liver itself.

These conclusions are contrary to those drawn by Farah and Smuskowicz[3] concerning the role of the rat's liver in respect to strophanthin. These authors found that the rat's liver adsorbed but apparently did not destroy strophanthin. The differences between their findings and ours, of course, may be due not only to the fact that different glycosides have been studied, but also to the fact that theirs was an in vitro, and ours an in vivo study of hepatic-glycoside relationships. Certainly to date, we also have not been able to detect any destruction of digitoxin by the *isolated* liver slice. This is not surprising when it is remembered that it is extremely doubtful if the metabolism of any cyclopentanophenanthrene compound proceeds efficiently in isolated liver slices after several hours.[11]

If there appears to be a potent extrabiliary process in the rat liver (and to a lesser extent in the rabbit liver) for the destruction of digitoxin there seems little evidence suggesting a similar capacity possessed by the liver of the dog[7] or of man. The latter, for example, continues to excrete via his kidneys[4] remnants of a single small dose of digitoxin for well over 14 days until about 40 per cent of the original amount is thus eliminated. It seems highly improbable that this very slow renal process would be utilized if a potent mode of hepatic excretion or destruction were at hand.

Summary

1) Quantitative studies were made of the hepatic excretion of digitoxin by the rat, rabbit, dog, and man. A small but significant fraction of the administered drug was detected in the bile of each species except man.

2) Intrahepatic destruction of digitoxin was found to occur in the rat and rabbit but not in the dog.

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Respiratory Burns with Special Reference to Pulmonary Edema and Congestion

By Domingo M. Aviado, Jr., M.D., and Carl F. Schmidt, M.D.

The functional changes in respiration, circulation, blood composition and blood temperature were investigated in anesthetized dogs that were subjected to the inhalation of steam. The pathogenesis of the accompanying pulmonary congestion and edema was analyzed by measurements of: (a) pulmonary blood flow, (b) pressures in pulmonary artery and vein, (c) pulmonary blood (P^{32}) volume, (d) electrical (AC) resistance of the lungs, and (e) edema fluid of the excised lung. The peculiarities of the pulmonary circulation that were demonstrated by bleeding and blood infusion explain the difficulties of correcting the congestion that regularly preceded thermal edema.

THE susceptibility of the lungs to various forms of injuries is attested by the numerous publications on blast injury,[1, 2] phosgene poisoning,[3] and dust inhalation.[4] The subject of respiratory burns has been conspicuously neglected. The available publications consist entirely of pathologic reports of suspected clinical cases[5–7] and of experimental burns.[8] It is the primary aim of this report to analyze the important functional changes resulting from steam inhalations particularly those of respiration, circulation, blood temperature and blood constituents. Pulmonary congestion and pulmonary edema were so prominent in this investigation that attempts were included to understand, in greater detail, the behavior of the pulmonary circulation by radioactive technic[9, 10] and by electrical resistance measurements.[11, 12] These methods have revealed certain interesting characteristics of the lung circulation that were further explored for therapeutic possibilities of this, so far fatal, thermal edema.

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Methods

Dogs under morphine (2 mg. per kilogram) and chloralose (50 to 100 mg. per kilogram) were used exclusively. A metal tracheal cannula was inserted and connected to the manifold represented in figure 1. By opening and closing the appropriate stopcocks, the animal was allowed to inhale room air or steam at atmospheric pressure. The following measurements were taken repeatedly before, during and after each inhalation: (a) temperature of the blood in the abdominal aorta by inserting through one femoral artery a polyvinyl catheter containing a copper constantan thermocouple (40 S. W. G.), the electromotive force developed being measured by a (Rubicon) galvanometer; (b) electrocardiogram; (c) carotid arterial pressure by a mercury manometer or by a Lilly electrical capacitance manometer[13]; (d) respiration by pneumograph and by collecting expired air in a spirometer; (e) analysis of femoral arterial blood (Paritol* as anticoagulant) for oxygen and carbon dioxide content,[14] total hemoglobin,[15] plasma hemoglobin,[15] plasma specific gravity expressed as plasma protein[16] and hematocrit.[17]

The following additional measurements were taken in a selected number: (f) cardiac output estimated by the standard direct Fick method including catheterization of the pulmonary artery and analysis of expired air[18]; (g) measurement (by a saline manometer) of pressures in a cannulated pulmonary lobar artery and a lobar vein with the chest subsequently closed over the connecting tubes; (h) measurement of volume of blood in the lungs by means of radioactive erythrocytes,[10] described briefly

* The Paritol was kindly supplied by Dr. Joseph Seifter, Wyeth Institute of Applied Biochemistry, Philadelphia.

in figure 13; and (i) pulmonary electrical resistance described in detail below under Part III-A.

All animals were autopsied and the lungs were further analyzed by (a) gross examination; (b) histologic section; (c) weighing for per cent moisture based on wet and dry weights; and (d) chemical analysis for blood content and edema fluid content, described in detail in the appendix. The analyzed lungs were also obtained from perfusion experiments described in figure 12.

Results and Discussion

Part I. Pathologic Physiology of Steam Inhalations

Steam was selected in this investigation following the suggestion by Moritz, Henriques and McLean[8] that moist heat is more effective

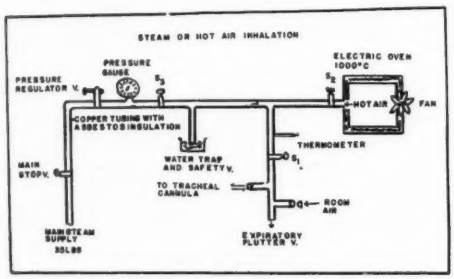

FIG. 1. Manifold for tracheal inhalation of (a) Room air while stopcock S_1 is closed; (b) Hot air while S_2 and room air outlet are closed and while S_1 and S_2 are open; and (c) Steam while S_2 and room air outlet are closed and while S_1 and S_3 are open. Steam of 35 pounds pressure from the generator of the building is reduced to atmospheric pressure beyond S_2 and any excess pressure is released through the safety valve and water trap. Expired air can freely leave the manifold through flutter valve that is made of heat resistant fabric.*

than dry heat in inducing pulmonary burns. The following preliminary experiments were designed to study events in an intact dog, with full realization that lung burns normally coexist with burns of the upper respiratory passages and of the skin.

Skin burns were induced in three dogs by flushing steam into a metal chamber harboring the whole body excluding the head. Such a procedure was always accompanied by a prominent hyperpnea, bradycardia and carotid hypertension, which started before any rise in arterial blood temperature. The reflex nature of these early effects was further demonstrated by noticing a similar response when the burn was limited to one hindleg with its circulation occluded temporarily. The sensory impulses from the leg were not transmitted entirely by the spinal nerves because the response could still be elicited after cutting the sciatic, obturator and femoral nerves. The sensory sympathetic fibers evidently participated in the stimulation of respiration and circulation following burns of the skin.

As soon as steam was allowed to enter the respiratory passages in three other dogs, the response was strikingly different. Nasal inhalation of steam caused a marked inhibition of respiration. When steam was forced into the upper respiratory tract (by a tracheal cannula directed towards the nose), the inhibition of respiration was not as impressive as when steam was administered to the lower tract of the same dog (by a second tracheal cannula directed towards the lungs). Although almost all of the experiments that will now be described consisted of direct tracheal steam inhalation, the functional changes can be regarded as fairly typical of those encountered when an anesthetized intact animal is allowed to inhale heat, particularly steam.

A. Blood Temperature. The outcome in the 18 dogs that were subjected to tracheal steam inhalation is summarized in table 1. All dogs died within two hours after injury. There was no correlation between the duration of inhalation (12 to 120 seconds) and the time of death chiefly because the amount of steam inhaled was limited by the respiratory response.

The estimation of the uptake of steam by measuring arterial blood temperature brings into consideration not only the amount of steam inhaled, but also the efficiency of the circulatory system to conduct the heat absorbed from the alveolar spaces. The maximum rise in aortic blood temperature ranged from 0.3 to 12.6 C. A close comparison of these rises and the survival of the dogs (table 1) did not show any relation. It was therefore apparent that the amount of injury and its outcome can

* Silicon Rubber (Type SR150) was supplied by Mr. Elbridge Stockwell, Jr., of the Stockwell Rubber Co., Philadelphia.

TABLE 1.—*Summary of Dogs Subjected to Tracheal Steam Inhalations, Arranged in the Order of Duration of Survival*

Dog No.	Date 1951	Weight (Kg.)	Burn Sec.	Maximum rise in Bl. Temp. (C.)	Death (mins. after burn)	Tracheal Froth	
						Onset (mins.)	Death after onset (mins.)
Circulatory Deaths							
407	7-30	10.4	30	12.6	1		
402	7-25	11.4	15		2		
405	7-27	11.1	60	4.9	2		
399	7-23	17.3	120	3.0	71		
			55	0.3	3		
428	8-15	9.1	15	2.1	19		
			30	4.0	2		
Respiratory Deaths							
420	8-8	13.0	30	2.2	3		
426	8-14	10.0	12	6.7	8		
416	8-6	11.1	35	1.4	35		
			30	7.4	10		
Pulmonary Edema							
398	7-20	19.3	90		42		
			90		31		
			60		15	1	14
423	8-9	11.8	20	6.9	27	25	2
413	8-2	8.9	15		28	27	1
424	8-10	12.3	15	7.5	29	4	25
403	7-26	10.0	60	4.7	40	27	13
410	8-1	10.4	30	5.8	45	8	37
419	8-7	10.0	40	7.1	45	7	38
425	8-13	14.1	15	3.1	83	58	25
418	8-7	14.1	30	2.6	101		
			40	4.9	63	7	56
438	8-27	17.0	15	8.8	120	15	105

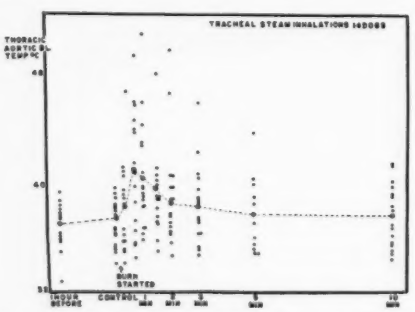

FIG. 2. Blood temperature of aorta following steam inhalations. The circles connected by dotted line represent mean temperature in 14 dogs.

not be judged by aortic temperature changes alone.

The temperature curves were interesting in other respects. After the quick rise and slow fall, the arterial temperature was stabilized in three minutes to a new level that averaged about half a degree higher than the control (fig. 2). In two dogs, this higher level was manifested by additional thermocouples introduced into the pulmonary artery, the left ventricle and the rectum. Oxygen consumption at this time was not higher than before burns so that increased metabolism was not a plausible explanation. The fever started too early to be explained by a systemic response as encountered after severe injuries and infections. The cause was suggested by extending the observations of blood temperature before the tracheotomy. Blood temperature remained constant, but the insertion of the cannula caused a gradual rise averaging 0.6 C. per hour. It was inferred that the omission of the upper passages interfered with normal pulmonary heat loss, and that burning the trachea and lungs interfered even more. Other examples of corresponding impairment of respiration and circulation as a result of lung burns will be mentioned below.

B. Respiratory and Circulatory Events During Inhalation. The most consistent effects during steam inhalation were apnea, bradycardia, and a rise in carotid blood pressure (fig. 3). They were often interrupted in a minute or so by polypnea and tachycardia. No single mechanism could entirely explain them. At least three were identified:

1. Respiratory reflexes from the lungs: The apnea was originated by a reflex mechanism, because (a) it could not be elicited after vagotomy, and (b) it started before there was a noticeable rise in arterial temperature. The latter observation suggested further that the receptors were not far from the lungs and consisted of one or all of the following groups: (a) sensory receptors in the respiratory passages, (b) stretch receptors in the alveolar wall, and (c) pressoreceptors and drug receptors in the pulmonary veins.[19] Although these reflexes could not definitely be implicated, the known stimuli to each group (ammonia inhalation,

lung inflation, veratridine injection, respectively) became ineffective when tested after the inhalation of steam. The permanent damage to these receptors is reflected by two other observations. Subsequent inhalations did not cause an apnea (fig. 3). The slow and deep breathing which followed the apnea and which persisted long after the initial steam inhalation, simulated the effects of vagotomy and continued after cutting both vagi.

2. Reflexes causing bradycardia: The slowing of the heart rate during inhalation started as abruptly as the apnea but was distinct from

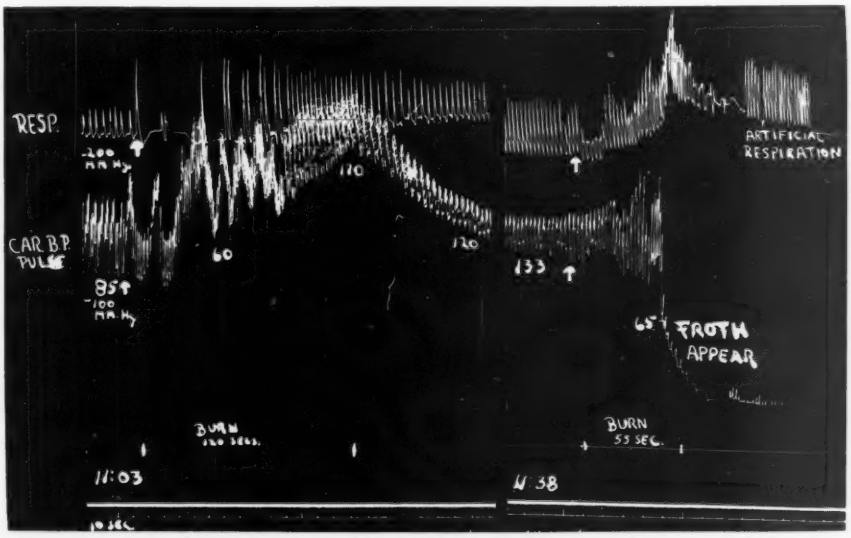

FIG. 3. Apnea, bradycardia and carotid arterial hypertension after first steam inhalation. The second inhalation caused less prominent respiratory inhibition and immediate circulatory failure. Other pertinent data of dog 399 are in tables 1, 3, and 5.*

it. As long as the vagi were intact, repeated inhalations could still cause bradycardia but no apnea. Identification of the receptors involved was not possible in these preparations.

3. Medullary stimulation: The carotid hypertension coincided very closely with the rise and fall of blood temperatures before and after vagotomy. This rise in blood pressure was due to a generalized vascular constriction because cardiac output during this response was lower than the control value (table 2). No other attempt was made to distinguish between constriction caused by central vasomotor stimulation and by direct peripheral action. In most instances the peak in carotid pressure was accompanied by other signs of medullary stimulation, namely tachycardia and polypnea.

The exposure of the entire pulmonary circulation to heat caused hemolysis more extensive than that encountered in peripheral burns. Plasma hemoglobin values were as high as 1.0 Gm. per 100 cc. initially and dropped slowly to lower levels (table 5*). The maximum hemolysis encountered in each dog was related neither to the severity of respiratory and circulatory effects, nor to the early onset of death, which will now be described.

C. Early Deaths: Circulatory and Respiratory Failures. Five of the 18 dogs died of circulatory failure within three minutes after lung burns. Blood pressure fell to zero, while the animal continued breathing (fig. 3). Vagotomy in two dogs effectively eliminated the severe bradycardia, but the resulting tachycardia did not cause the blood pressure to recover. The death was not caused by vagal

* At the request of the editor, tables 5 and 6 are being omitted but will be supplied on request.

influences. For some unknown reasons, these burns had severely damaged the circulatory system.

The other three early deaths were characterized by primary cessation of respiration. Low arterial blood oxygen saturation was characteristically present before burning probably because of difficulties in closure of the chest. The even lower oxygen saturations after the burns did not stimulate respiration as in a normal animal. The resulting depression signified a respiratory center and/or chemoreceptors that could not compensate properly for anoxemia.

TABLE 2.—*Effects of Steam Inhalations on Cardiac Output, Oxygen Consumption, Pulmonary Blood (P^{32}) Volume and Pulmonary Arterial Pressure*

Measurements	Dog No.	Before	Immed. After	Δ	% Δ
Cardiac output, cc./min.	423	1213	834	379	−31.2
	425	1618	1445	173	−17.0
	428	1266	1057	209	−16.5
			862	404	−31.9
			747	519	−40.1
Oxygen consumption, cc./min.	423	124	119	5	−4.1
	425	137	139	2	+1.5
			126	11	−8.0
	428	84	79	5	−5.9
			63	21	−25.0
Pulmonary blood volume; radioactive counts per minute, average for five minutes	420	1310	1390	80	+6.1
	426	1080	1790	710	+65.8
	413	1000	1800	800	+80.0
	424	1000	1480	480	+48.0
Pulmonary arterial pressure, cm. H_2O	418	24	31	7	+29.2
		20	40	20	+100.0
	416	37	45	8	+21.6
		35	50	15	+42.8

The early respiratory deaths were characterized further by the appearance after death of froth in the tracheal and bronchial passages. The remaining 10 dogs that are described in the next section, developed froth before death and presented an opportunity to study the pathogenesis of pulmonary edema.

Part II. Pathogenesis of Thermal Edema

The first appearance of fluid in the tracheal cannula regularly occurred within half an hour after the inhalation. A conspicuous sign at this time was an increased respiratory minute volume chiefly due to an increased depth with the rate constant and was characterized by visible participation of the accessory muscles of respiration (fig. 4). The other measurements helped in understanding the causes of the hyperpnea. Blood oxygen saturations remained essentially normal and carbon dioxide content was decreased until just before the animal died. A central stimulation by known chemical stimulants therefore was unlikely. Vagotomy in two dogs did not interfere with the hyperpnea. The only re-

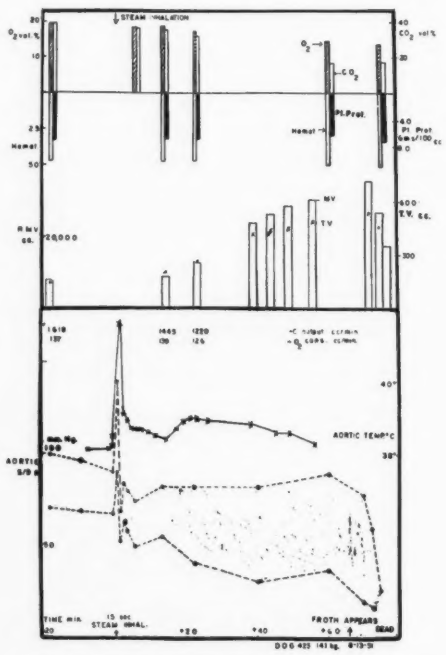

FIG. 4. Events accompanying onset of pulmonary edema after steam inhalation. From top to bottom are blood O_2 and CO_2, hematocrit and plasma protein, respiratory minute and tidal volumes, cardiac output, oxygen consumption, aortic blood temperature, and aortic pulse pressures with a Lilly manometer. Other pertinent data for dog 425 are in tables 1, 2, 3, 4 and figure 10.

maining possibility was that the hyperpnea was a reflex that was activated by edema and was mediated by the sensory sympathetic nerves. The existence of such receptors has been suggested by others.[20–23]

As soon as edema started, death was inevitable within two hours. The tracheal fluid was found to have a specific gravity equal to about 80 per cent of that of plasma. The accumulation of fluid and plasma protein in the lung parenchyma was further reflected by an increasing hematocrit, blood hemoglobin content, and plasma specific gravity (table 5*). As expected, blood oxygen content and saturations became low enough to explain the fatal outcome.

A. Changes in Pulmonary Circulation. The mechanism of pulmonary edema was studied by the radioactive measurements of pulmonary blood volume. Four dogs showed an increase in pulmonary blood volume amounting to 60 to 80 per cent of control value (table 2). This increase is not due to increased pulmonary flow because cardiac output always fell after pulmonary burns. It therefore involved the stagnant blood rather than flowing blood. The cause of this congestion was further investigated by measuring pulmonary vascular and cardiac pressures.

There are three ways of producing pulmonary congestion with decreased pulmonary blood flow: (a) Failure of the left side of the heart; this was not present here because left auricular pressure did not rise after burns (fig. 5). The observed increase in pulmonary arterial pressure did not support (b) a dilatation of the pulmonary vessels. On the other hand, it favored (c) a constriction of the pulmonary veins with accumulation of blood in the capillaries and arterioles.

The demonstration that pulmonary congestion always preceded the appearance of tracheal fluid establishes the importance of venous and capillary pressure in the causation of edema and casts doubt upon increased capillary permeability as a sole cause. The amount of pulmonary congestion as measured by the radioactive experiments was influenced by other factors. One dog that died of immediate circulatory failure did not show a rise in counts (table 2). When the other dogs lived long enough to develop edema, the radioactive counts invariably increased. Pulmonary venous constriction was maximum immediately after the burn when pulmonary arterial pressure was highest. On the other hand, congestion (radioactive counts) was maximum 5 to 10 minutes later after carotid blood pressure had recovered from the initial hypertension and before the appearance of tracheal fluid (fig. 6). This suggested that congestion was not solely due to the direct action of heat on the pulmonary vessels (venous constriction), but also

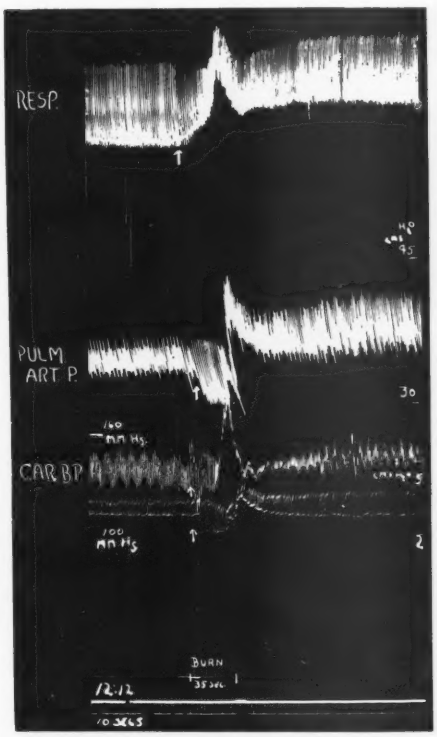

FIG. 5. Effects of steam inhalation on respiration, pulmonary arterial pressure, carotid blood pressure and left auricular pressure (top to bottom). Other pertinent data for dog 416 are in tables 1, 2, 3, and 5.*

* At the request of the editor, tables 5 and 6 are being omitted but will be supplied on request.

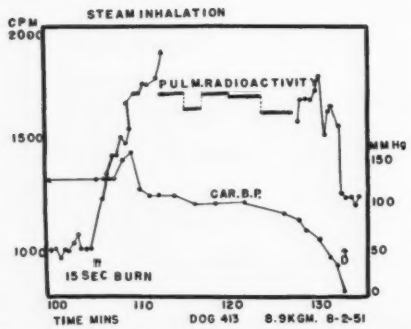

FIG. 6. Pulmonary blood radioactivity and carotid blood pressure after steam inhalation until death (D). Other pertinent data for dog 413 are in tables 1 and 2.

due to unidentified factors, that were probably acting in vicious cycles.

B. Pathologic Changes in the Excised Lungs. The significant autopsy findings of dogs that were subjected to steam inhalations were confined to the lungs. The gross picture was a constant and characteristic one, as typified in figure 7. The tracheal and bronchial mucosal linings showed marked capillary injection and contained a foamy sanguinous fluid. The lung tissue was boggy, and when cut, revealed multiple small focal areas of hemorrhage centered about the respiratory bronchioles.

Microscopic examination showed that the greatest pathologic changes were centered

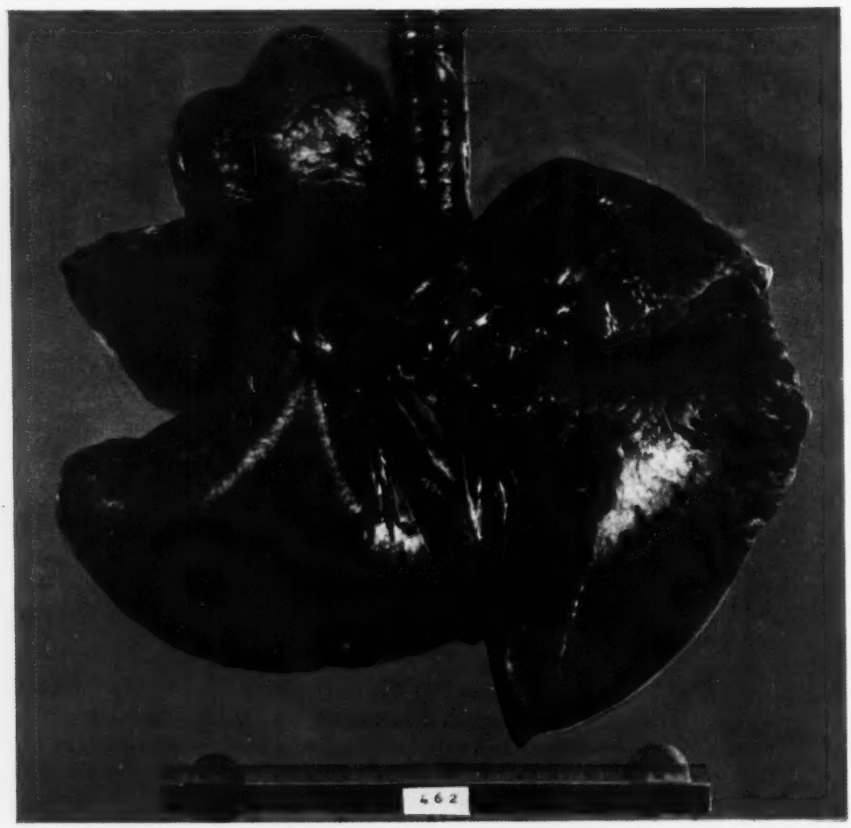

FIG. 7. Lung excised immediately after death of dog subjected to nasal steam inhalation for one minute. Tracheal fluid appeared in 20 minutes; animal died 65 minutes later. Dog 462, 161. Kg., 11–27–51.

(The use of color in this illustration is made possible by a grant from Winthrop-Stearns, Inc., to the publication fund of the American Heart Association.)

about the respiratory bronchioles and that the most peripheral portions of each lobule showed minimal involvement (fig. 8). The most striking finding was that of edema fluid which occupied the more central alveolar sacs. The adventitial lining of the venules showed a peculiar swelling or "cuffing" by edema fluid (figs. 8, 9, 10). Capillary engorgement with or without the frank extravasation of erythrocytes into the surrounding tissues was prominent (fig. 10). Ruptures of the alveolar walls were seen in some slides (fig. 9).

The morphologic changes largely confirm the importance of congestion in the development of edema. The "cuffing" of the pulmonary veins by edema fluid illustrates further that the veins are affected before edema spreads to alveolar spaces. The instantaneous appearance of congestion and edema can be deduced from the dogs that died immediately after burning without fluid in the passages (fig. 8).

C. Chemical Changes of the Excised and Perfused Lungs. Further confirmation of lung pathology was offered by quantitative measurements of the excised lungs (see appendix and table 3). There were significant differences in total weight and total moisture content between lungs of dogs killed with Nembutal or bled to death, and lungs from the burned dogs. The greater moisture in the burned lungs was due partly to more blood and chiefly to more edema fluid.

Although these measurements on severity of congestion and edema do not help in understanding the reasons for the differences in behavior among the various living dogs, the measurements become more informative when they are compared with measurements obtained from perfused lungs. The excised lung (one side) from a freshly killed dog was perfused for one hour with its own blood at normal arterial pressure (25 mm. Hg) but slightly higher than normal venous pressure (10 mm. Hg). (Method described in fig. 12.) Four such lungs were found to be heavier; they contained more blood, but the normal amount of edema fluid when compared with the corresponding unperfused side. Still another similar group of lungs with additional burning during perfusion, exhibited the usual increased blood volume

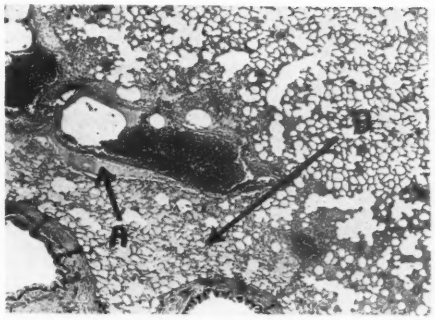

FIG. 8. Histologic section of lung obtained from dog dying two minutes after 60 second steam inhalation. Perivascular "cuffing" with edema fluid (*A*) and peribronchiolar alveolar edema (*B*) are prominent. (×10.) Other pertinent data for dog 405 are in tables 1, 3, 4, and 5.*

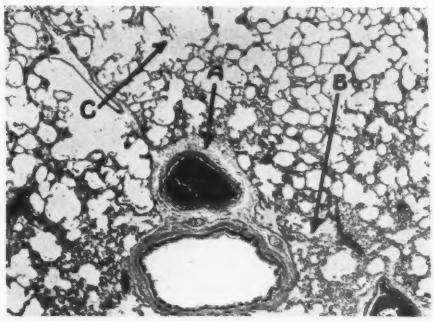

FIG. 9. Lung section obtained from dog that developed tracheal froth 25 minutes after burn and died two minutes later. Emphysema (*C*) is represented, in addition to perivascular "cuffing" (*A*) and alveolar edema (*B*). (×10.) Other pertinent data for dog 423 are in tables 1, 2, 3, and 5.*

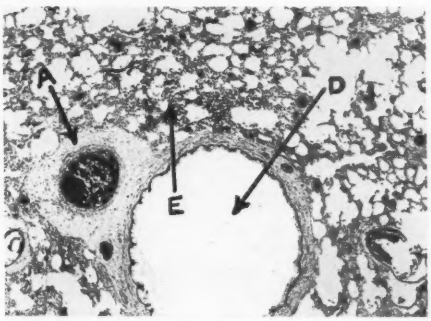

FIG. 10. Lung section from dog 425 which is depicted also in figure 5. There is marked arteriolar and capillary engorgement (*E*), bronchiolar dilatation (*D*), and perivascular "cuffing" with edema fluid (*A*). (×10.)

* At the request of the editor, tables 5 and 6 are being omitted but will be supplied on request.

TABLE 3.—*Chemical Analysis of Excised and Perfused Lungs for Total Weight (Wt.), Per Cent Moisture (Per Cent M), Cubic Centimeters Blood Per 100 Gm. Lung (BVL) and Per Cent Edema Fluid (Per Cent E. F.)*

Dog Side	Body Wt. (Kg.)	Wt.	% M	BVL	% E.F.	Dog Side	Body Wt. (Kg.)	Wt.	% M	BVL	% E.F.
Normal Lungs						Lungs after Steam Inhalation					
392L	11.6	31.57	75.83	16.97	61.81	398R	19.3	234.10	87.88		
						L		169.71	87.25		
393R	17.0	93.98	81.68								
L		93.88	81.74			399R	17.3	264.71	77.57		
						L		172.85	78.38		
395R	14.3	68.44	77.45								
L		58.48	78.08			402R	11.4	123.71	83.09		
						L		99.54	83.94		
396L	14.5	44.94	78.22								
						403R	10.0	145.17	85.28	15.42	72.89
400L	17.7	42.35	78.28			L		87.82	84.76		
401R	7.7	62.79	81.48	34.84	52.09	405R	11.1	137.02			
L		51.36	81.87								
						410R	10.4	216.50	87.16	12.91	76.27
406L	12.7	73.73	79.33			L		180.15	87.80		
411R	13.9	61.76	78.76	14.97	66.82	416R	11.1	93.37	83.54	22.75	64.18
L		45.42	80.09								
						418R	14.1	181.02	77.65	16.49	62.20
412L	11.4	32.05	79.36	18.59	64.10						
						423L	11.8	76.64	82.45	12.03	72.72
421L	14.0	48.08	78.64	18.39	63.23						
						425L	14.1	136.42	84.77	16.83	71.11
429L	16.1	80.41	77.84	15.94							
						428L	9.1	60.13	85.16	12.01	74.88
442R	19.0	29.20*	77.52	15.94	59.02						
						441R	5.9	53.85	84.34	18.25	69.96
446R	29.6	73.60	80.75	29.06	55.09	L		58.20	86.24	19.03	70.93
458R	10.0	25.49*	78.37	45.61	38.82	443R	15.9	104.20	82.40	15.94	70.40
L		23.45*	77.05	42.28	40.38	L		98.30	85.30	15.94	72.34
467R	25.0	125.2	80.44	21.20	62.71						
L		99.35	79.46	20.98	61.91						
Average R		67.56	79.56	26.93	55.76	Average R		155.36	83.21	16.96	69.32
		±32.40	±1.73	±11.94	±9.82			±65.15	±3.64	±3.33	±5.33
L		55.77	78.91	22.19	58.29	L		113.98	84.60	15.17	72.40
		±24.12	±1.70	±9.99	±1.01			±47.13	±2.67	±3.09	±1.59
Perfused Congested Lungs						Perfused Burned Lungs					
442L	19.0	31.91*	83.19	15.94	64.69	392R	11.6	142.15	85.69	11.20	76.98
446L	29.6	42.05	79.96	27.20	55.94	421R	14.0	178.69	86.78	17.11	72.94
459L	8.2	55.96	81.77	22.19	63.90	427R	10.7	163.45	89.28	22.17	68.87
400R	17.7	223.77	75.55	38.86	42.57						
Average		88.42	80.12	26.05	56.77	Average		161.43	87.25	16.83	72.93

* Represents weight of lower lobe only; weight of entire side otherwise.

ut considerably more edema fluid (table 3). ncreased capillary permeability by burning is herefore necessary for congestion to lead to dema in the perfused lung.

Summary of Causation of Thermal Edema. t least two factors are actively causing the ulmonary edema after steam inhalations: a) congestion and (b) increased capillary ermeability. The permeability changes were emonstrated in burned perfused lungs but heir exact role in intact animals remains to be roven. The prominence of congestion is based n observations in animals with closed chest, nd on morphologic and chemical analysis of xcised lungs. The immediate congestion is nitiated, at least, by pulmonary venous constriction which was the only possible interpretation from the following: increased lung blood (P^{32}) volume, decreased pulmonary flow, increased pulmonary arterial pressure and normal left atrial pressure. The persistence of congestion after pulmonary arterial pressure has become normal means that other factors besides venous constriction were causing the congestion. The "cuffing" of the pulmonary veins with edema fluid (seen histologically) may be one of such factors. The control of pulmonary blood volume was next investigated as an attempt to remedy this congestion.

Part III. Control of Pulmonary Blood Volume

Our present information on pulmonary blood volume is based on direct measurements in perfused lungs,[24, 25] and on estimates by dye dilution[26–28] and by vital capacity[29] in man. The radioactive technic has offered an additional means of supplementing our understanding of the pulmonary circulation. The last group of experiments now to be described was designed to elucidate the factors affecting pulmonary blood volume as related to the correction of pulmonary congestion and edema. A concomitant problem was the development of a method to measure the progress of pulmonary edema in the living animal so that any beneficial effect of the selected procedure can be assessed not only on the congestion (by radioactive method) but also on the edema.

A. Detection of Edema by Alternating Current Resistance. One of the greatest difficulties in the study of pulmonary edema is its detection before the relatively late appearance of fluid in the passages. Methods that involve histologic examination become undesirable when continuous observations on a living animal are preferred. The estimation of fluid changes by electrical methods was first applied by Lambert and Gremels in 1926 to the heart-lung preparation.[11] Its application to the whole animal with closed chests was undertaken systematically in the following manner:

1. Excised Lung. The original method proposed by Lambert and Gremels required the application of direct current voltage on copper electrodes inserted into the lungs. Polarization of such electrodes in an excised lung was easily demonstrated by noticing one to be polished and the other tarnished. The direct current measurements were indications of an electrolytic electromotive force, which was independent of the position of electrodes. We have minimized polarization by two modifications: (a) using platinum electrodes (size 26), and (b) measuring alternating current resistance with the signal source from an oscillator, an alternating current bridge for balancing the impedance and an oscilloscope as a null point indicator. The alternating current resistance was affected by distance between the platinum electrodes inserted into the lung. For a sample spacing, the resistance beyond a frequency of 20,000 cycles per second remained essentially constant (fig. 11). This level was selected for all subsequent readings because it represented a reasonable compromise of all other factors, namely, problems of shielding and ease of operation. At this frequency the excised lung was found to be sensitive to the introduction of 5 cc. fluid into the cannulated artery and of 10 cc. air into the trachea, but not to induced temperature changes (fig. 11).

2. Perfused Lung. The sensitivity of alternating current resistance measurements to air and fluid changes in the lung was further demonstrated in the isolated perfused lung. A dog was bled to death, the right lung was excised, and cannulas were inserted into bronchus, artery and left auricle for negative ventilation and perfusion (fig. 12). In each of two preparations, stopping arterial flow to reduce the amount of blood in the lung caused an increase in alternating current resistance while the development of edema (by alloxan) caused a fall in resistance. The effects of blood flow changes are important because they emphasize the fact that alternating current resistance is sensitive to fluid changes but cannot distinguish between blood and edema fluid.

3. Intact Dogs. The experience in intact animals confirms the above observations. The chest was opened and the platinum tips were tied into two points of one lobe. With the chest closed, the

respiratory movements were reflected in time and in magnitude on the oscilloscope. Although the movements were difficult to follow, they were an assurance that electrical connections to the lung were complete. The initial values of alternating current resistance ranged from 0.167 to 1.17 ohms, which meant variable spacing among different dogs. The absolute values in each dog were meaningless, hence relative per cent changes were utilized in expressing the results. The control values every three minutes for one hour had a variation of 3 per cent or less. Changes that were greater than this value were regarded as significant.

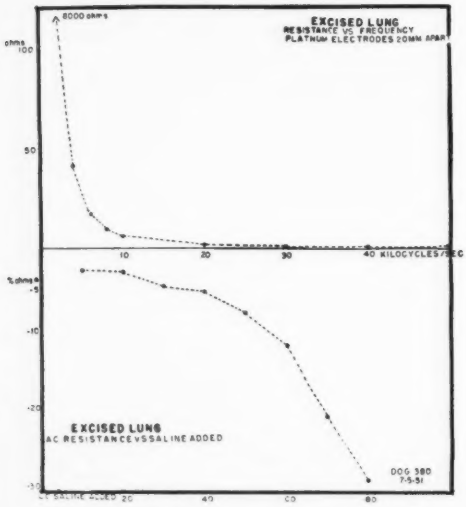

FIG. 11. *Top:* Alternating current resistance (ordinate) plotted against changing frequency (abscissa) obtained from excised lung of dog 386. An oscillator (Hewlett-Packard 200 C.) was used as a signal source, an alternating current bridge for balancing the impedance (General Radio Type 650 A), and an oscilloscope as a null point indicator (Dumont Type 304). *Bottom:* Effect of introducing saline into cannulated pulmonary artery (with vein closed) on the resistance using 20,000 cycle frequency. The same excised lung was used.

Two other ways of inserting electrodes were tried: (a) blind insertion through a needle (2 inch 19 gauge) with or without fluoroscopic guidance, and (b) incorporation of one electrode in a pulmonary arterial catheter inserted under the fluoroscope as far out as possible into a lobar artery and the other electrode tied to the adjacent chest wall. Although these measurements did not involve opening the chest, the placement was not fully certain until at autopsy. With proper precautions, these two systems gave results as satisfactory as tying the electrodes into the exposed lung.

The pulmonary alternating current resistance measurements obtained from dogs breathing spontaneously are tabulated in table 4. The animals dying after steam inhalation showed a larger percentage fall in values than those dying of other causes (bleeding, asphyxia, Nembutal) without evidences of edema. The utilization of this technic for detecting the exact onset of edema was not successful. Although the resistance dropped immediately after the steam inhalation, it was difficult to exclude the possibility that such changes were due to accompanying congestion. As will next be described, alternating current resistance

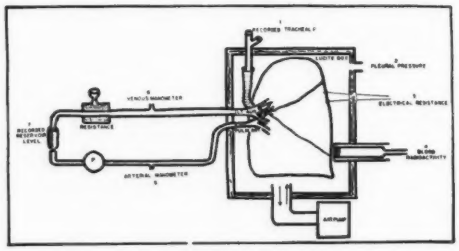

FIG. 12. Isolated lung perfusion. Dog under Nembutal was bled to death and trachea, left auricle and pulmonary artery of one side were cannulated. The opposite lung was ligated at its hilus and the remaining lung was excised for perfusion with a Dale Schuster pump. The collected blood with Paritol was pumped into the cannulated artery while the venous outflow was returned to the arterial reservoir. The vascular pressures were controlled by output of pump and by Starling resistance on the venous tubing. The lung was inflated by intermittent positive and negative pressure in the lucite box*, properly warmed at 40 C.

detected blood volume changes in the lung after bleeding and infusion and it was mainly for this purpose that the measurements proved most useful.

B. Effects of Bleeding and Blood Infusion. The simplest way of reducing blood volume in the lungs was by decreasing the available circulating blood. When an animal was bled in sufficient amounts (by way of femoral artery 15 cc. per kilogram) pulmonary blood radioactivity fell while alternating current resistance increased. This reduction in lung blood volume

* The lung chamber was made by Mr. D. W. T Cochrane of this laboratory

remained until the lost blood was replaced. Bleeding in repeated smaller amounts (5 cc. per kilogram three times) did not affect all the measurements significantly although the total blood lost was equal to a larger bleeding. The repeated bleedings happened within a period of 15 minutes so that the entrance of tissue fluids to replace the lost blood seemed improbable. Hematocrit remained essentially constant.

The pulmonary arterial pressure reflected closely the amount of blood lost. It decreased equally after one large bleeding and after three smaller bleedings (fig. 13). The logical explanation for the maintenance of pulmonary blood volume when blood is lost slowly is that blood is shifted from the peripheral depots to the lungs. This compensation was not clearly reflected by pulmonary arterial pressure changes although the dilatation of pulmonary capillaries to accept the shifted blood may coexist with diminished cardiac output to cause a fall in pulmonary arterial pressure. The disappearance of this compensating mechanism after vagotomy suggested a neurogenic factor. Electrical stimulation of peripheral end of vagus before or after bleeding did not change the pulmonary blood measurements. The importance of the vagi in this compensatory adjustment may not depend on pulmonary vasomotor fibers,[30] but may depend on the cardiopulmonary pressoreflex (vagal afferent) fibers that have been shown to participate in the maintenance of peripheral circulation during bleeding.[31]

TABLE 4.—*AC Resistance Measurements: Initial and Terminal Values for Dogs Dying of Pulmonary Edema, and Dogs Dying of Other Causes. Platinum Electrodes Were Tied into Lung Tissue (L-L), Introduced Blindly through Chest Wall into Lung (L-W), or Utilized Pulmonary Arterial Catheter and Chest Wall (A-W)*

Dog No.	Date 1951	Body Weight (Kg.)	Method	Cause of Death	Initial Resistance (ohm)	Terminal Resistance (ohm)	% Δ
405	7–27	11.1	L-L	Burn	.564	.551	−2.31
			L-W		.486	.393	−22.0
418	8–7	14.1	L-L	Burn	.764	.636	−16.8
420	8–8	13.0	L-L	Burn	.918	.723	−21.1
424	8–10	12.3	L-L	Burn	.568	.426	−24.9
393	7–17	17.0	L-W	Nembutal	.541	.528	−1.9
395	7–18	14.3	L-L	Bleeding	.110	.132	+22.3
			L-W		.184	.233	+26.6
414	8–2	12.3	L-L	Bleeding	.118	.350	+198.0
422	8–9	18.9	L-L	Nembutal	.350	.552	+86.9
431	8–16	7.7	L-L	Asphyxia	.655	.662	+1.6
433	8–20	19.3	L-L	Bleeding	1.170	1.000	−14.5
			A-W		1.050	.945	−10.0
435	8–22	17.3	A-W	Nembutal	.294	.330	+11.0

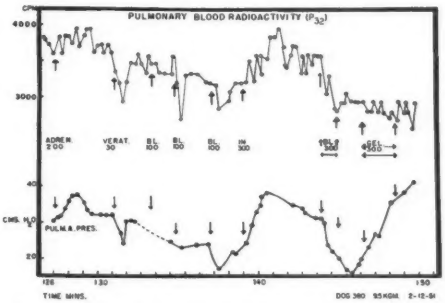

FIG. 13. Continuous recording of lung blood radioactivity (upper) and pulmonary arterial pressure (lower) after repeated small bleeding (100 cc. three times), one large bleeding (300 cc.), and blood infusion. The effects of gelatin, adrenaline and veratridine are included. Measurement of lung blood volume from the pleural surface with a counter (Amperex 150NB) encased in an aluminum channel that is protected with a thin rubber membrane to allow complete closure of chest. The radioactivity of the erythrocytes tagged with phosphorus^{32} (5 cc. blood equilibrated with 0.1 mc. and washed) was registered continuously on a scaler (Technical Associates GS_4) attached to an inkwriting oscillograph (Brush Development BL202). All results were expressed as counts per minute (cpm) after correction for background.

Blood infusion caused the converse picture, that is, increased pulmonary radioactivity and decreased alternating current resistance (table 6*). This response was present when the infusion followed a small compensated or a large noncompensated bleeding. A closer analysis of continuous radioactive and pulmonary arterial pressure measurements revealed that the increased radioactivity and increased pulmonary arterial pressure after a blood infusion lasted for several minutes, and outlasted the accompany-

* At the request of the editor, tables 5 and 6 are being omitted but will be supplied on request.

ing rise in carotid pressure. After pulmonary measurements have completely recovered to normal levels, cardiac output was essentially unchanged. It appeared as though the infusion caused a temporary storage of blood in the lung by venous constriction to explain the increased arterial pressure and increased lung blood volume with the cardiac output not higher than expected. This venous constriction was not affected by vagotomy. A similar response of the pulmonary arterial pressure has been reported in man.[32]

After steam inhalation, bleeding or infusion did not significantly change the already high pulmonary radioactivity. The three burned dogs subjected to repeated bleeding died with usual pulmonary congestion and edema as described in Part II.

Final Comment

The difficulties in treating pulmonary congestion and edema after steam inhalation can be explained on a twofold basis: (a) the compensating mechanism that normally stabilizes lung blood volume, and (b) injury to pulmonary vessels by heat, particularly by direct venous constriction and early "cuffing" of the pulmonary vein. As long as these factors are active, blood-letting does not offer any advantage. The prolonged congestion seen after blood infusion characterizes the pulmonary vessels as being able to store blood so that the contraindication of infusions in respiratory burns and other forms of pulmonary congestion is understandable.

The treatment of the other causative factor, that is, increased capillary permeability remains as an alternative approach in the therapy of pulmonary edema associated with respiratory burns. The problem of detecting early edema in a living animal remains unsolved. Findings in the experiments reported here have suggested a new means to the solution. The radioactive technic is now being extended so that blood volume is measured by P^{32} tagged erythrocytes while edema fluid is measured by I^{131} tagged plasma albumin.

Summary and Conclusions

The effects of respiratory burns were investigated in anesthetized dogs. The following functional disturbances were observed:

(a) The most prominent effect of tracheal steam inhalation is an immediate apnea that is followed in a minute by polypnea. This inhibition arises from lung receptors which are permanently damaged after activation by steam.

(b) The bradycardia that accompanies the apnea is also a reflex arising from extrapulmonary receptors, unidentified in these experiments.

(c) The uptake of heat is reflected by a sudden rise in aortic blood temperature. A central medullary stimulation by warm blood is the best explanation for the short-lasting peripheral vasoconstriction, polypnea and tachycardia, which all coincided with the peak of arterial blood temperature rise. The stabilization of temperature at a higher level is caused by the loss of heat-eliminating function of the burned lungs and passages.

(d) Blood hemolysis is more extensive than that encountered in skin burns.

(e) Froth in respiratory passages appears within half an hour after steam inhalation. One prominent accompanying sign is an increased respiratory minute volume. The increased depth is best explained by reflexes mediated by the sympathetic nerves from the lungs. After prolonged edema, anoxia becomes severe and blood analyses show low oxygen content and saturation, high blood hemoglobin, high hematocrit and high plasma specific gravity.

All 18 dogs died within two hours after tracheal steam inhalation. Although the five dogs that died of immediate circulatory failure did not show fluid in the tracheal cannula, congestion and edema were seen grossly and histologically in all the excised lungs. Congestion is a constant accompaniment of thermal edema. Radioactive measurements of lung blood volume show an immediate congestion after burning. This is due to a venous constriction which is the only possible interpre-

tation from increased radioactivity, decreased pulmonary flow, increased pulmonary arterial pressure and normal left atrial pressure. The chemical analysis of perfused lungs for edema fluid shows that increased capillary permeability by heat is a necessary accompaniment for pulmonary congestion to cause edema.

A pulmonary venous constricting mechanism is also initiated by blood infusion such that blood is stored for some time after it is injected intravenously. This response persists after vagotomy.

An attempt to treat pulmonary congestion after steam inhalation by arterial bleeding was unsuccessful partly because of a neurogenic mechanism that stabilizes the pulmonary blood volume at a constant level. Bleeding causes a shifting of blood from the peripheral depots into the lungs.

The electrical resistance method of Lambert and Gremels has been adapted for intact dogs. Several modifications in technic and interpretations are described. The alternating current resistance measures fluid changes in the lung but cannot distinguish between blood and edema fluid. It can measure lung blood volume changes.

A method that can detect early edema in a living animal is still wanting.

Appendix

Chemical Analysis for Blood Volume and Edema Fluid in an Excised Lung. Principle: The edema fluid is calculated as the difference between total moisture and bloody moisture of the excised lung. This estimated edema fluid includes normal tissue fluid.

Measurements:

L_T = weight of lung cut proximal to ligated hilus and prevented from drying (Gm.).

L_W = wet weight of aliquot portion after whole lung is minced in Waring Blendor for 10 minutes (Gm.).

L_D = dry weight of L_W after 24 hours in 150 C. oven (Gm.).

B_W = wet weight of accurately measured cardiac blood (Gm./100 cc.).

B_D = dry weight of B_W, similarly dried (Gm./100 cc.). (All above weighings were on an analytic balance, expressed to nearest 0.01 Gm.)

H_B = hemoglobin content of B_W; duplicate analysis by colorimetric technic[15]; (Gm./100 cc.).

H_L = hemoglobin content of aliquot portion of minced lung by the method originally described by Greenberg and Erickson.[33] Dr. Werner Kalow has introduced the following modifications that were found necessary for congested and edematous lung: (a) Instead of cutting small pieces of lung with a pair of scissors, the whole lung was ground into a brei with a Waring Blendor thus providing a representative sample; (b) After washing with acetone and adding acid mixture, the acid hematin was most effectively extracted by mechanical shaking of tubes for one hour at room temperature. Duplicate analyses of same lung were found to have a standard deviation of 0.142 Gm., and an average variation of 7 per cent. Results were expressed in Gm. hemoglobin per 100 Gm. lung.

Calculations:

$$\text{Per cent Total Moisture of Lung} = \frac{L_W - L_D}{L_W} \times 100$$

(also total moisture Gm./100 Gm. lung).

$$\text{Blood Volume in Lung (cc. blood/100 Gm. Lung)} = \frac{H_L}{H_B} \times 100$$

$$\text{Per cent Blood Moisture in Lung} = \frac{(B_W - B_D) \times \text{Blood Volume in Lung}}{100}$$

(also blood moisture Gm./100 Gm. lung).

Edema Fluid in Lung (Gm./100 Gm. Lung) = % Total Moisture − % Blood Moisture in lung.

Sample values of normal, edematous and perfused lungs are in table 3.

Acknowledgments

We are deeply grateful to Albert H. Niden, David M. Seymour and Leonard J. Epstein for their patient assistance in the performance of most of these experiments. We also wish to acknowledge the help of Geraldine F. Croft and Helen D. Shelley in the blood and lung analysis, of Joseph E. Paul in the electronic equipment, of Dr. W. C. Yakovac in the histologic examination, and of Dr. W. Kalow in developing the modifications for the analysis of lung hemoglobin.

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Induced Hypercholesterolemia and Atherogenesis

By IRVINE H. PAGE, M.D., AND HELEN B. BROWN, PH.D.

An attempt has been made to elicit atherosclerosis in rats by duplicating as far as possible those conditions which in other animals are atherogenic. By making the rats hypothyroid and feeding cholic acid and cholesterol, severe hypercholesterolemia and abnormal beta-lipoproteins appeared along with heavy lipid infiltration of the kidneys, liver, heart and aorta. Aortic and coronary atherosclerosis might have been expected in rats exposed to so much atherogenic material in the blood, but it was not found. Despite lipid infiltration in the intima of the vessels, no appreciable tissue reaction to it occurred; we believe the lack of tissue response is one of the chief causes for the failure of atherosclerosis to develop. Thus tissue response and receptivity to lipid deposition seem to be important mechanisms in atherogenesis.

INDUCED hypercholesterolemia, when sufficiently prolonged, results in atherosclerosis in many animals. Dogs and especially rats are resistant; resistance in dogs, however, can be overcome by feeding large amounts of cholesterol during induced hypothyroidism. Even this drastic treatment has not been effective in rats.[1, 2a]

Thus it still seemed probable that if a sufficient hypercholesterolemia could be elicited in rats and sustained for long periods, atherosclerosis might result in them as in dogs. After many trials, the combination of I^{131} induced hypothyroidism and feeding of cholesterol and cholic acid was adopted to this end. By these means extreme hyperlipemia was produced and sometimes maintained for a year. The effect of such treatment on the blood vessels, liver, heart and kidneys is described in this report.

EXPERIMENTAL PROCEDURES

The experiments were conducted in three series (table 1).

The first series was a pilot experiment. Three groups of 11 to 16 adult male and female rats each, the animals being 2 to 7 months of age and weighing 150 to 500 Gm., were fed a diet of dog chow with the following supplements: group 1, none; group 2, 4 per cent cholesterol;* group 3 a, b, 2 per cent cholic acid and 4 per cent cholesterol. The rats in group 3, sections a and b, were studied at different times, the second group (3 b) being of uniform age and weight at the beginning of the experiment. The normal controls (group 1) were killed at intervals during the experiment; the experimental groups (2 and 3) in this first series were allowed to remain on the supplements until near death. Weights were observed and tail blood sampled monthly; whole blood cholesterol was determined on individual rats. At death, the liver was weighed and sampled for cholesterol content; specimens were taken from the liver, kidney, heart and aorta for microscopic examination after staining with hemotoxylin-eosin or Sudan IV. Cholesterol in blood and liver was determined by the Schoenheimer-Sperry method.[3]

The second series consisted of six groups of male and female rats; two control groups with four to six normal rats and four experimental groups with 8 to 16 rats made hypothyroid by intramuscular injection of 1 microcurie of radioiodine (I^{131}).[4] These rats were fed a basal diet of dog chow with the following supplements by groups: normal control, group 4 none and 2 per cent cholic acid for group 5; hypothyroid experimental groups, group 6 none, 2 per cent cholic acid for group 7, 4 per cent cholesterol for group 8 and 2 per cent cholic acid and 4 per cent cholesterol for group 9. These rats weighed from 200 to 250 Gm. and were between 2 and 2½ months of age. Weights were observed weekly; tail blood samples from four rats chosen in rotation within each group were taken every third week at first, and every fourth week thereafter. This bleeding program was adopted because of tail lesions in the hypothyroid rats. Total serum cholesterol was determined

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* Cholesterol used in these experiments was very kindly furnished by Merck and Company (Dr. Augustus Gibson).

on pooled blood samples from each group by the method of Abell, Levy, Brodie and Kendall.[5] At 8 months the survivors were bled to death from the carotid artery and the alpha and beta lipoprotein fractions were determined in the ultracentrifuge by Dr. Lena A. Lewis with the method of Gofman and his co-workers[6] as modified by Green, Lewis and Page.[7]

In the third series, the basal diet of groups 4 to 9 was a modified Sherman diet[8] consisting of 25 per cent dried whole milk, 67 per cent whole wheat flour, 5 per cent yeast, 2 per cent sodium chloride, 1 per cent calcium lactate. Wheat bran amounting to 6 per cent of the total mixture was added to the cholic acid supplemented diets.

TABLE 1.—*Diet, Treatment, Number and Weight of Rats*

Group	Basal diet	Supplements		State of Thyroid	Number of Rats				Weight			
		4% cholesterol	2% cholic acid		Beginning	6 mo.	10mo.	14mo.	Beginning	Range Gm.	Final	Range Gm.
Series 1												
1	Dog chow	—	—	Normal	14	—	—	—	175	150–200	329	272–425
2	Dog chow	+	—	Normal	11	7	5	1	365	215–514	362	245–460
3a	Dog chow	+	+	Normal	14	7	4	4	200	140–300	300	245–405
3b	Dog chow	+	+	Normal	16	12	7	7	175	150–200	252	205–295
Series 2												
					Beginning	6 mo.	8 mo.					
4	Dog chow	—	—	Normal	4	4	4		175	150–200	320	260–395
5	Dog chow	—	+	Normal	6	5	5		175	150–200	275	210–395
6	Dog chow	—	—	Hypo	8	7	7		175	150–200	290	215–385
7	Dog chow	—	+	Hypo	8	8	8		175	150–200	220	165–265
8	Dog chow	+	—	Hypo	16	13	13		175	150–200	290	215–355
9	Dog chow	+	+	Hypo	16	12	5		175	150–200	180	135–330
Series 3												
1	Dog chow	—	—	Normal	4	4	4		175	150–200	370	270–445
2	Dog chow	+	—	Normal	10	8	8		175	150–200	270	210–372
3	Dog chow	+	+	Normal	10	8	7		175	150–200	230	180–295
4	Modified Sherman	—	—	Normal	4	3	3		175	150–200	335	235–435
5	Modified Sherman	—	+	Normal	8	5	5		175	150–200	240	195–310
6	Modified Sherman	—	—	Hypo	5	3	3		175	150–200	210	200–235
7	Modified Sherman	—	+	Hypo	10	6	4		175	150–200	185	150–265
8	Modified Sherman	+	—	Hypo	6	3	3		175	150–200	215	190–240
9	Modified Sherman	+	+	Hypo	12	8	8		175	150–200	160	135–200

RESULTS

The diets were not conducive to longevity. Dog chow proved somewhat better than the modified Sherman diet, especially when cholic acid was given (table 1). The diarrhea which often resulted from cholic acid diets was found to be controlled by addition of 6 per cent bran. The severity of hypothyroidism was estimated from the dry scaliness of the skin over the animal and the loss of hair, especially over the forepart. Autopsy proved that deprivation of active thyroid tissue had not been complete.

1. *Blood.* High serum total cholesterol—of the order of 250 to 500 per cent of normal—was found in normal rats fed cholesterol plus cholic acid. But the combination of hypothyroidism with cholic acid and cholesterol feeding even further elevated the heightened cholesterol levels to about 1000 mg. per 100 ml. in series 2 and 2000 mg. per 100 ml. in series 3. The values equal those in cholesterol-fed chicks, rabbits and thiouracil-treated dogs, all of which develop atherosclerosis.

It is of interest that in our rats fed basal diets for a period of eight months, neither hypothyroidism nor cholic acid alone altered serum cholesterol. In most animals a rise may

be anticipated from hypothyroidism, although this is not invariable.[9]

According to Lewis, Green and Page[10] normal rat's serum contains lipoproteins, determinable in the ultracentrifuge with flotation rates at a density of 1.21, of classes −S 8–9 and 15 (that is, alpha lipoproteins) and a beta$_1$ lipoprotein of the 30 class. The concentration of alpha lipoproteins is about 100 mg. per 100 ml. and the beta$_1$, 30 mg. per 100 ml. The same pattern occurred in our hypothyroid rats. Feeding of cholic acid, cholesterol or their combinations (table 2) resulted in the appearance of other beta lipoproteins, that is, $-S_{1.21}$ 40–70 (similar to Gofman's S_f 12–20 class) and −S> 70. It should be noted that the rat's normal alpha and beta lipoproteins were unchanged by this type of supplemental feeding.

TABLE 2.—*Serum Total Cholesterol and Lipoprotein Fractions* ($-S_{1.21}$)

Group	Basal Diet	Supplements		State of Thyroid	No. Observations	Serum Total Cholesterol				Lipoproteins					
		4% cholesterol	2% cholic acid			Mean mg.%	Stand. Error	Range Low mg.%	Range High mg.%	No. Rats	β (70)	β (40–70)	β_1 (30)	α (15)	α (9)
Series 1															
1	Dog chow	—	—	Normal	44*	75‡	±2.5	43	114	—					
2	Dog chow	+	—	Normal	30	119	±7.2	81	220	—					
3a & b§	Dog chow	+	+	Normal	64	200	±9.0	71	424	—					
Series 2															
4	Dog chow	—	—	Normal	10†	82	±3.3	56	100	4	—	—	12	Spreading	125
5	Dog chow	—	+	Normal	10	91	±4.5	70	109	4	—	—	10	6	64
6	Dog chow	—	—	Hypo	10	85	±5.2	61	116	7	—	—	25	4	83
7	Dog chow	—	+	Hypo	10	120	±8.1	88	163	13	—	16	20	16	84
8	Dog chow	+	—	Hypo	10	161	±13.2	131	250	5	38	36	20	10	100
9	Dog chow	+	+	Hypo	10	698	±57.1	453	960	8	330	130	33	51	66
Series 3															
1	Dog chow	—	—	Normal	8†	67	±2.8	54	77	2	—	—	19	12	71
2	Dog chow	+	—	Normal	8	96	±5.7	86	128	8	111	11	15	—	96
3	Dog chow	+	+	Normal	8	319	±43.7	216	595	7	184	112	30	45	142
4	Modified Sherman	—	—	Normal	11	103	±4.2	84	126	3	—	—	28	36	154
5	Modified Sherman	—	+	Normal	21	111	±4.3	83	167	7	—	—	19	—	118
6	Modified Sherman	—	—	Hypo	11	104	±4.6	80	135	3	—	—	36	40	150
7	Modified Sherman	—	+	Hypo	22	143	±4.9	124	165	4	85	56	8	35	66
8	Modified Sherman	+	—	Hypo	10	441	±14.3	169	638	4	250	119	33	—	75
9	Modified Sherman	+	+	Hypo	20	1486	±70.5	914	2050	8	803	267	93	±	281

* Values for first eight months given; thus comparable to date given in series 2 and 3.
† Pooled serum samples from four rats.
‡ Individual samples of whole blood.
§ 3a and b. Blood values combined.

These new beta lipoproteins were under 90 mg. per 100 ml. in the hypothyroid rats fed cholic acid alone, increasing two to three times when cholesterol alone was fed, and then further greatly increasing when cholesterol and cholic acid combined were fed. In the latter

groups of rats, the −S 40–70 classes were increased four to five times and the −S > 70, 7 to 10 times.

2. *Liver.* Gross changes in appearance of the liver occurred only in the cholesterol-fed rats. Cholic acid elicited no change from normal until cholesterol was fed along with it, when the liver became fatty. In the hypothyroid rats

FIG. 1. The liver of a hypothyroid rat after eight months on a cholic acid, cholesterol-supplemented feeding.

fed cholic acid and cholesterol, the liver was greatly enlarged and the lipid changes were so extreme the liver became almost colorless (fig. 1).

The bile ducts of normal rats fed the mixture of cholesterol and cholic acid were engorged with bile and gave the appearance of being gall bladders, an observation noted by Loeffler in cholesterol and cholic acid-fed mice.[11] No engorgement occurred in hypothyroid rats.

Cholic acid feeding in cholesterol-fed animals changed the proportionate weight of liver to body from 3 per cent to 7 per cent.

Total hepatic cholesterol increased from 0.2 per cent wet weight in normal and hypothyroid rats to 7 per cent in normal and 14 per cent in hypothyroid rats fed cholic acid and cholesterol. The increase was chiefly in the cholesterol ester with surprisingly little rise in free cholesterol.

The amount of total cholesterol in these fatty livers differed as much as 20 per cent in the different parts of the liver itself as compared with variations of 3 per cent in the livers of normal rats. This spotty distribution was almost characteristic of the cholesterol-fatty liver.

Histologic examination confirmed the heavy and uneven lipid deposition in the hypothyroid, cholic acid–cholesterol fed animals. Cholic acid alone elicited only slight fatty infiltration with a few fat-filled cells in the midzone and occasional areas of necrosis.

3. *Kidneys, Heart and Aorta.* Histologic examination of these organs showed significant lipid deposition only in the hypothyroid rats fed cholic acid and cholesterol. The renal tubular cells were well loaded with lipid and the glomeruli occasionally contained some lipid. The muscle and arteries of the heart were also well infiltrated with lipid.

The intima of the aorta exhibited diffuse heavy accumulation of lipid particles occasionally penetrating into the media. It is noteworthy that no foam cells or intimal proliferation was present in any of the aortas studied.

DISCUSSION

The purpose of this investigation was to determine whether atherosclerosis could be produced by extreme elevation of lipids for long periods of time. A variety of methods have been tried over the past six years to achieve severe lipemia and finally the combination of hypothyroidism, cholesterol and cholic acid feeding was chosen. This achieved our purpose in that serum total cholesterol values as high or higher than those which elicit atherosclerosis in rabbits, chickens and dogs were produced. The time hyperlipemia was maintained was also comparable. Therefore we had a reasonable expectation of obtaining aortic and coronary atherosclerosis. It did not occur. Rather, a

heavy, diffuse infiltration of the intima without tissue reaction to it was observed.

It seems to us that in this failure of the tissue to react to the lipid infiltration lies one of the keys to the problem of atherosclerosis. We pointed out a number of years ago that the receptivity of tissues for lipid deposition was altered by iodide feeding.[12] It is not alone the composition of the plasma which determines the amount of atherosclerosis but the receptivity and response of the tissues to lipid that decides the appearance of atherosclerosis. Since completion of our experiments, a preliminary report concerning production of atheromatous lesions in rats indicates that old age and hypertension may increase the susceptibility of the arteries to lipid infiltration.[13]

We have reason from both chemical and ultracentrifugal analysis of the blood to expect atherogenesis. Not only is the cholesterol excessively high but the beta lipoproteins, which Lewis and Page[14] have incriminated in the genesis of vascular disease, make their appearance in abundance. Further, the molecular classes of lipoproteins believed by Gofman[6] to be atherogenic, are present. Thus, on all counts, from study of the blood atheroma should have occurred.

The relatively simple anatomic structure of rat's aorta may possibly contribute to the failure of atherogenesis. But a much more penetrating analysis of its anatomy is indicated before this facet can be properly evaluated.

TABLE 3.—*Hepatic Cholesterol*

Group	Basal Diet	Supplements		State of Thyroid	Liver		Total Cholesterol		Free Cholesterol		
		4% cholesterol	2% cholic acid		No.	% Body Wt.	% Wet Wt.	Range	% Wet Wt.	Range	% Total
Series 1											
1	Dog chow	—	—	Normal	14	3.8	0.177	0.147– 0.096	—		
2	Dog chow	+	—	Normal	9	3.9	0.784	0.200– 0.205	—		
3a	Dog chow	+	+	Normal	11	7.5	7.46	2.03 –13.0	—		
3b	Dog chow	+	+	Normal	13	4.7	3.49	1.2 –10.2	—		
Series 2											
4	Dog chow	—	—	Normal	4	2.9	0.265	0.161– 0.486	.171	.126–.245	65
5	Dog chow	—	+	Normal	6	3.2	0.367	0.136– 0.823	.261	.115–.479	71
6	Dog chow	—	—	Hypo	7	2.5	0.217	0.136– 0.457	.171	.082–.407	78
7	Dog chow	—	+	Hypo	8	2.8	0.394	0.210– 1.59	.314	.102–.524	80
8	Dog chow	+	—	Hypo	13	2.7	1.96	0.142– 7.75	.244	.114–.392	12.5
9	Dog chow	+	+	Hypo	5	7.1	13.4	7.50 –16.3	.655	.431–.762	4.9
Series 3											
4	Modified Sherman	—	—	Normal	3	3.2	0.205	0.183– 0.235	.176	.138–.252	84
5	Modified Sherman	—	+	Normal	5	3.2	0.287	0.174– 0.352	.097	.112–.300	69
6	Modified Sherman	—	—	Hypo	4	2.7	0.205	0.170– 0.260	.160	.126–.198	78
7	Modified Sherman	—	+	Hypo	9	2.7	0.387	0.205– 0.578	.299	.156–.453	77
8	Modified Sherman	+	—	Hypo	4	3.2	2.67	0.290– 4.85	.248	.207–.297	9.2
9	Modified Sherman	+	+	Hypo	11	6.9	14.4	9.40 –26.2	.599	.311–.950	4.1

The appearance of lipid in the rat's aorta is like that in rabbits 24 hours after a single intravenous injection of 0.5 Gm. of cholesterol.[2b] Lipid is visible in the endothelial cells and intercellular spaces, but no intimal reaction has occurred. Within 72 hours cellular proliferation and foam cells appear and the process of cleaning up the debris continues for several weeks. In rats even after eight months of extreme hypercholesterolemia, no foam cells or proliferation were observed.

It is of interest that cholates, glycocholates and, to a lesser extent, desoxycholates aid in

the production of hyperlipemia.[15, 16] It has been presumed for some time that they aid in the absorption of cholesterol and it was on this notion, along with the choleic acid principle, that prompted us to use these salts.

Some years ago we concluded that alteration in the receptivity of the tissues to lipid deposition was a factor in atherogenesis.[12] We now add the further one of tissue reaction to the infiltrated lipid. Failure to react with production of foam cells, fibrosis, and other characteristic change leaves the lesion of atherosclerosis incomplete. The rat thus provides an interesting example for study of the critical problem of tissue response.

Friedman and his associates[17-23] are making a penetrating study of the association of cholate to cholesterol metabolism, and have already demonstrated some interesting relationships. They have shown that hypercholesterolemia develops in rats with the bile duct ligated. It is heightened by ingestion of cholate and is associated with increased plasma cholate. Hypercholesterolemia was induced in normal rats by intravenous administration of cholate, indicating that it is a result of the increased cholate concentration.

In considering this relationship between cholate and hypercholesterolemia, it is important that no hypercholesterolemia developed in our normal rats fed cholic acid alone, while hypercholesterolemia occurred in hypothyroid, cholic acid fed rats. Hypothyroidism has been shown by Rosenman, Friedman and Byers[24, 25] to reduce cholesterol excretion in the bile, thus simulating two features present in the rat with ligated bile duct, namely, reduced cholesterol excretion and hypercholesterolemia. This difference between normal and hypothyroid rats in their reaction to cholic acid probably lies in the cholate concentration of blood.

Not only plasma but hepatic cholesterol is increased when cholates, glycocholates and desoxycholates are given to cholesterol-fed animals[16, 26]; hepatic cholesterol may also increase in animals given cholic acid alone.[11] In hypothyroid rats fed cholic acid and cholesterol much more cholesterol accumulates in the liver than accumulates in chickens, rabbits and hypothyroid dogs. This high hepatic cholesterol, along with the high serum lipids and fatty infiltration of the tissues, is reason to expect atherogenesis.

Summary and Conclusions

1. Normal and hypothyroid (I^{131} treated) rats were fed a basic diet of dog chow or modified Sherman diet supplemented with 2 per cent cholic acid and 4 per cent cholesterol, alone and together, for eight months. Serum total cholesterol, serum lipoprotein ($-S_{1.21}$) and hepatic cholesterol were measured; histologic examination of the liver, kidney, heart and aorta was made.

2. Feeding cholic acid and cholesterol to hypothyroid rats elicited severe hypercholesterolemia, averaging 1500 mg. per 100 ml., and abnormal serum beta lipoproteins, $-S_{1.21}$ 40–70, averaging 270 mg. per 100 ml. and $-S_{1.21} > 70$, 800 mg. per 100 ml. Accompanying these blood changes were very fatty livers, twice normal size, containing 14 per cent choesterol, mostly as ester, and heavy lipid infiltration of the kidneys, heart and aorta. In spite of the lipid penetration into the intima of the aorta, there was no formation of foam cells or intimal proliferation.

3. The condition present in these hypothyroid rats fed cholic acid and cholesterol was conducive to atherogenesis and similar to that in cholesterol-fed chickens, rabbits and hypothyroid dogs in which atherosclerosis develops. There was no atherosclerosis in the rats.

5. The resistance of the rat to atherosclerosis is not dependent upon ability to block lipid infiltration but rather upon the lack of tissue response to the infiltrating lipid.

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Hemodynamic Studies in Rheumatic Heart Disease

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Hemodynamic studies were made in 42 patients with rheumatic heart disease with various valvular lesions and in different stages of cardiac function. These studies include observations not only at rest, but also during exercise, following the acute administration of Digoxin, and after recovery from failure. The relationship between symptomatology and hemodynamic findings were considered and the importance of differentiating between mechanical block and left ventricular myocardial failure as causes for pulmonary artery hypertension is stressed.

EQUIPPED with the newer technics which permit accurate measurements of cardiocirculatory function in man, clinical investigators have attempted to establish a clearer and more complete definition of the effects of congenital and acquired heart disease. The pressure patterns encountered in advanced rheumatic heart disease were first described by Bloomfield and co-workers.[1] More recently in other clinics the investigation of symptomatic rheumatic heart disease has continued, emphasizing particularly patients with mitral valvular lesions.[2–11]

In the present report an effort has been made to assess a number of types of rheumatic heart disease including the asymptomatic patient. Measurements were made at rest in a wide clinical spectrum of cases. These were supplemented in some subjects by other studies, such as response to exercise, acute digitalization, and serial measurements before and following recovery from heart failure. A companion paper to this present one will deal with the effects of surgical commissurotomy.[12]

Method

The 42 patients presented in this report were studied with the use of the cardiac catheterization technic. Measurements included determination of cardiac output, blood volume and peripheral arterial, pulmonary arterial, right ventricular and auricular pressures. In addition to data obtained in the basal resting state without premedication, measurements were also made in some patients following acute digitalization or after exercise. The procedure followed in the Digoxin studies has been described elsewhere as have the criteria employed for the evaluation of the results.[13, 14]

In the exercise studies, after the determination of cardiac output, blood pressures and blood volume in the resting basal state, the period of exercise was begun. The patient, supine on the fluoroscopic table, alternately flexed and extended his lower extremities as if pedaling a bicycle. Flexion of the thigh on the trunk was accomplished without resistance and did not exceed a 90 degree angle in order to eliminate insofar as possible compression of the abdominal viscera. Extension of the lower extremities was effected against resistance supplied by two members of the team, each one of whom pushed against one of the patient's feet. The leg motion was maintained at a regular rate, each leg being flexed and extended 10 to 12 times per minute. The duration of exercise was 7 to 23 minutes as indicated in table 3. There was no attempt made to achieve a maximum effort or to standardize this exercise test from patient to patient, therefore speed, duration and resistance varied with the ability of the patient to perform the exercise. No untoward reactions occurred in any of the subjects during this procedure. In most instances a double lumen catheter was used in these studies, in order that pressures might be obtained in the pulmonary artery and right ventricle without displacement of the catheter, because movement of the catheter may disturb the steady state. Hence if a double lumen catheter was not employed, no ventricular tracings were obtained during the exercise period. The cardiac output was determined only after 5 to 12 minutes of exercise. The expired air was collected in a Tissot gasometer for two minutes. During the middle minute of air collection

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simultaneous blood samples were drawn from the pulmonary and brachial arteries.

The determination of the cardiac output, using the Fick principle, demands a steady state which creates a problem whenever a change of state occurs, as for example the shift from rest to exercise. Therefore, in order to obtain a valid cardiac output under these circumstances, sufficient time must elapse to permit the patient to assume a steady state such that at the new level of activity an equilibrium is reached between the blood and gas phases in the lungs. This state is difficult to reach before three minutes of exercise for the following reasons: First, in our experience it usually takes at least one minute for the patient to assume the steady rhythmic performance of leg motion. Second, breath holding is a common accompaniment of the first minutes of exercise, thus altering the composition of the expired air and invalidating measurements of oxygen uptake in this period. Finally, it is not unlikely that there are temporary inequalities in blood flow early in exercise; for example, the initial increased venous return from the exercising limbs with a low oxygen content, would create a larger arteriovenous difference and indicate a lower cardiac output than actually exists.

In order to ascertain the time at which, using the type of leg exercise described above, a steady state of gas exchange was achieved, a separate study[15] was made in cardiac patients to determine the respiratory gas exchange ratio (in former terminology, the respiratory quotient) of the expired air, and the oxygen consumptions at 2½ to 3¼, 4 to 5½, 6 to 7½, 8 to 9½, and 10 to 11½ minutes of exercise. The gas samples were analysed in a 0.5 cc. Scholander gas analyzer. At two and one-half to three and one-fourth minutes all the patients showed a very low respiratory gas exchange ratio and variable oxygen consumptions as compared with later samples. The respiratory gas exchange ratios and oxygen consumptions in the last three periods of exercise were constant however (see fig. 1) and the values of the respiratory gas exchange ratios approached or were slightly higher than the control resting values, as would be expected during muscular work. It appears, therefore, that determinations of cardiac output during this type of exercise are valid only if made five minutes or more after the onset of exercise. The above study justifies the assumption that a steady state of exercise had been reached at the time that the cardiac output was measured in the rheumatic patients here reported (table 3), inasmuch as measurements of oxygen consumption were made only after five minutes of exercise. This assumption is strengthened by the fact that the respiratory gas exchange ratios obtained during the determination of the cardiac output (table 3) were equal to or slightly higher than the resting figures.

In order to evaluate the reaction of the cardiac patients to this type of stress, it is necessary to define the normal response. Although normal subjects vary considerably in their response to exercise, one can say that a rough estimate of the expected increase in blood flow per 100 cc. increase in oxygen consumption is at least 600 cc. for the mild type of exercise performed.[15] The stroke volume also increases. Pulmonary artery pressures do not rise above normal unless there is more than a two-and-one-half fold increase in blood flow[16] and the right ventricular diastolic or filling pressure probably does not increase above 5 mm. Hg during such effort. These are, of course, measurements made with reference to atmospheric pressure, and do not take into account the intrathoracic pressure.

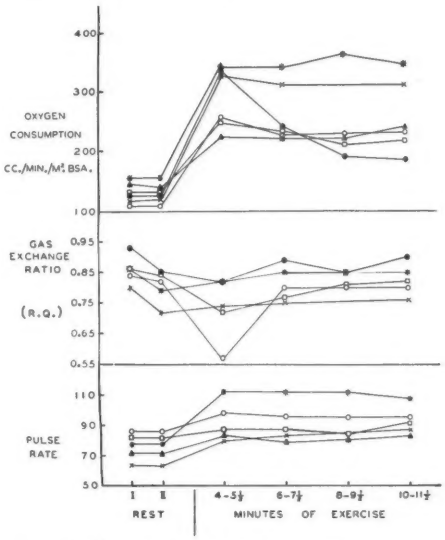

FIG. 1. Changes in oxygen consumption, the gas exchange ratio (respiratory quotient) and pulse rate prior to, and after assumption of, a steady state of exercise. (For discussion see text.)

Estimation of pulmonary blood volume was not included in this study since the accuracy of available methods to measure it remains open to question. While it is acknowledged that it would be of considerable interest to attempt to differentiate between the effects of pulmonary vascular disease and mechanical block at the mitral valve in these patients, no attempt was made to secure the "pulmonary capillary" pressure since its exact nature under pathologic conditions affecting the pulmonary circulation is in doubt. Furthermore, movement of the catheter back and forth in the pulmonary vascular tree may disturb the steady state. It was therefore considered preferable to secure tracings in the pulmonary artery and right ventricle under the most favorable circumstances.

No estimations of mitral orifice size, using the

proposed formulas,[5] were made inasmuch as the theoretic limitations of the calculation are many. The calculations are based upon continuous flow, and not the uneven, intermittent or even pulsatile flow which actually exists. It is assumed that the orifice is circular; if the valve is a slit, elliptical or funnel-shaped, or if its contour is uneven, or if there is significant mitral insufficiency, or if there is left ventricular failure with high diastolic pressure, the measurement will not be valid. Therefore at present it is believed more sound to base the evaluation of these rheumatic subjects on measurements other than this.

Material

The 42 patients included in this report were, with very few exceptions, hospitalized because of cardiac symptoms. Four were asymptomatic (cases 498, 564, 522, 637) and had never received any therapy directed toward the cardiovascular system. A fifth patient (case 650) was closely related to this group in that he had no signs or symptoms of diminished cardiac reserve, although he had had repeated hemoptyses associated with frequent upper respiratory infections. All of the other patients had had symptoms of pulmonary congestion in the past and in all but one of these (case 591) exertional dyspnea of greater or lesser severity was present at the time of study. Dyspnea at rest without evidence of right heart failure was present when catheterization was performed in five subjects (cases 633, 609, 664, 607, 459) but pulmonary rales were found in only two of these (cases 664, 607). Although a history of right heart failure was elicited in 14 patients (cases 627, 662, 633, 609, 552, 637, 535, 567, 642, 606, 559, 641, 595, 359), none of them showed evidence of it at the time of study. In many instances the evidence for right heart failure consisted of a history of minimal edema. Frank right heart failure associated with pulmonary congestion was present in 14 subjects when catheterized and it should be noted that in all but five (cases 555, 612, 538, 518, 387) it had been of long duration, despite digitalis and mercurial diuretics. Clinically it was difficult to ascertain whether or not right heart failure was present in one patient (case 618) with hepatomegaly, no edema, and no pulmonary congestion inasmuch as she had tricuspid insufficiency.

Finally a word remains to be said regarding hemoptysis. Of the 42 rheumatic cardiacs, 11 had a history of hemoptysis (cases 627, 633, 635, 567, 642, 622, 650, 518, 649, 595, 479). In two (cases 518, 479) bleeding had been severe enough to precipitate shock.

Clinically none of these patients was considered to have active rheumatic heart disease. The individual diagnosis, age, and sex, as well as information regarding digitalization, are given in tables 1 and 2. The diagnoses and classification were made according to accepted criteria[17] and represented the state of the patient at the time of study. Whenever a systolic murmur was present at the apex, a diagnosis of mitral insufficiency was made. In the absence of left ventricular enlargement and other signs of aortic valve insufficiency, and in the presence of marked pulmonary hypertension, a basal diastolic murmur was considered to be the result of pulmonic incompetence and classified as a Graham-Steell murmur. The diagnosis of tricuspid insufficiency appears in two forms in tables 1 and 2. Whenever *T. I.* appears without brackets, the diagnosis was made according to clinical criteria[17] and was confirmed by characteristic right auricular pressure tracings.[1] When *T. I.* is bracketed, the clinical manifestations were absent, but the right auricular pressure curves were nonetheless characteristic.

Many of the symptomatic patients received mercurial diuretics but no special study was made of this aspect of the problem, although it is recognized that the plasma volume would be affected by dehydration.

Discussion of Results

In this group of patients representing a variety of clinical material, consideration of the findings will be oriented around the solution of certain specific problems, among which are the following: the influence of specific valvular lesions, cardiac arrhythmias, and heart failure upon hemodynamic function; the possible relationship of symptomatology to the cardiodynamic findings; and finally the mechanisms whereby these alterations in function may occur.

Mitral Stenosis

The findings in patients with mitral stenosis, the commonest single valvular lesion in rheumatic heart disease, will be presented first. Although grouped primarily in table 1 on the basis of cardiac mechanism, the hemodynamic performance will be discussed in relation to symptomatology. Seven of the 16 patients had a sinus rhythm and nine auricular fibrillation (table 1, groups a and b).

No Symptoms. Although strictly speaking none of these 16 subjects was completely asymptomatic, one man (case 591) was relatively so, since he had been free of cardiac symptoms prior to a fist fight, which precipitated pulmonary edema, and was again asymptomatic when catheterized. Hemodynamic measurements at rest revealed an almost completely normal picture, the only alterations being a

slightly elevated pulmonary artery diastolic pressure and plasma volume. However, as can be seen in figure 2 and table 3, the response to exercise in this man was quite abnormal. For an increase in oxygen consumption of 83 per cent over the resting value, there was an 11 per cent increase in cardiac output and no increase—even a slight decrease—in stroke volume. This degree of exercise was accomplished with an increase of only 290 cc. of blood flow per 100 cc. increase in oxygen consumption. The subnormal rise in blood flow was accompanied by the early appearance of pulmonary hypertension in this man although he had had normal right heart pressures at rest. The pulmonary hypertension however was not sustained at a plateau during the whole exercise period, but declined toward its end and returned rapidly to pre-existing levels during the recovery period. The heart rate also rose during exercise, slowed during the later part of this period, and returned to control levels promptly during recovery. This performance during exertion suggests a possible explanation for the appearance of pulmonary edema in this man. The increased venous return massaged from the exercising limbs effected an increased ejection from the right ventricle and hence an increased pulmonary blood flow. Because of the shortened diastolic filling time accompanying a rise in heart rate and in the face of a mitral valve block, much of this blood was not transferred to the left ventricle, remaining in the lungs, increasing their blood volume and hence producing pulmonary hypertension early in exercise. Inasmuch as the increase in left ventricular filling was probably considerably less than that of the right ventricle, systemic blood flow did not rise. Ultimately, since the systemic flow regulates right ventricular venous return and output, these would decrease from earlier higher levels and no longer add to the pulmonary engorgement. In addition to changes in volume, a slowing of heart rate, such as occurred late in the exercise period, would further mitigate in favor of better outflow from the pulmonary bed. These mechanisms together would account for a decrease in pulmonary hypertension late in exercise and during recovery.

Symptoms on Exertion. Ten patients had had symptoms on exertion but were free of complaints at rest when studied (cases 620, 627, 663, 552, 635, 535, 567, 642, 622, 618). The hemodynamic pattern was fairly consistent. Pulmonary hypertension at rest was present in all but varied from mild (case 552) to severe (case 622). Cardiac output at rest was reduced in all but two individuals (cases 620 and 663). It is noteworthy that the right ventricular diastolic pressure was elevated in four (cases 620, 627, 622, 618) although in none of these was there clinical evidence of right heart failure. Furthermore two (cases 620 and 622) had never had a history of it. Plasma volume was slightly elevated in four subjects (cases 620, 635, 567, 618).

In order to amplify the hemodynamic picture which had been obtained by the studies at rest, the effects of acute digitalization were observed in one patient. In addition, this subject as well as four others were exercised.

The effects of Digoxin on the low cardiac output and minimal pulmonary hypertension of this 52 year old elevator operator (case 552) were determined after manifestations of pulmonary and peripheral congestion had cleared on bed rest alone. As can be seen in figure 3, the response to intravenous Digoxin was characterized by no change in cardiac output, pulmonary artery or right ventricular pressures, although there was a rise in stroke volume as a result of the slower heart rate. This reaction is seen in patients who are not in congestive failure[18] and suggests that the mild pulmonary hypertension was due to the mechanical effect of mitral stenosis. The second study in this subject was made two weeks later (fig. 3, table 5). In the interval he had been maintained on daily Digoxin and clinically there was no change in status. The pulmonary circulation pressures at rest and blood volume were unaltered. Cardiac output and particularly stroke volume, however, were higher on this second study. At this time the patient responded to exercise with a normal increase in blood flow, 590 cc. per 100 cc. increase in oxygen consumption (fig. 3, table 3). Accompanying this, pulmonary artery and right ventricular pressures as well as heart rate rose abruptly but returned swiftly

TABLE 1.—*Physiologic Data in 29 Patients with Rheumatic Heart Disease and Single Valvular Lesions*

Case Sex, Age, BSA	Diagnosis	Cardiac Index (L./min./M² BSA)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	Ventilation (L/min./M² BSA)	AV diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg.			TBV (cc/M² BSA)	PV (cc./M² BSA)	H'crt (%)
							cont. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle s/d			
Normal		3.12	72	131	3.40	4.2		96	120/70, 90	30/15, 10	30/5	2900	1600	45
					(a) *Mitral stenosis with sinus rhythm*									
#591. 28 yrs. M. BSA 1.69	EH. MS. NSR. IA.	3.54	70	159	4.79	4.5	16.4	98	113/69, 89	20/13, 16	20/3	3380	1910	44
#620. 43 yrs. M. BSA 1.68	*EH. MS. SA. IIC.	3.72	75	141	4.94	3.8	13.8	94	127/72, 94	35/19, 27	35/8	3170	1929	39
#627. 30 yrs. F. BSA 1.75	*EH. MS. (Graham-Steell) NSR. IIC	2.58	64	126	3.97	4.9	16.9	99	134/68, 94	60/23, 38	60/8	3048	1783	42
#663 37 yrs. F. BSA 1.39	*EH. MS. NSR. IIC	2.80	85	137	4.95	4.9	17.1	97	123/70, 93	46/26, 33	46/5	2563	1507	41
#664. 26 yrs. M. BSA 1.89	*EH. MS NSR. IIIC	3.10	96	161	5.23	5.2	17.8	91	112/73, 87	66/32, 43	66/2	3098	1573	49
#633. 28 yrs. M. BSA 1.76	*EH. MS. NST. Incomplete AV Block. IIIC.	3.23	102	159	6.19	4.9	15.1	82	92/58, 70	70/38, 55	70/1	3080	1698	45
#609. 34 yrs. M. BSA 1.58	*EH. MS.† NSR. IIID.	1.83	100	135	4.98	7.4	15.8	94	95/69, 80	108/59, 81	—	2880	1545	46
					(b) *Mitral stenosis with auricular fibrillation*									
#552. 52 yrs. M. BSA 1.77	EH. MS. AF. IIC.	2.00	79	108	4.41	5.4	17.6	95	105/75, 89	28/12, 19	28/4	3310	1755	47
#635. 39 yrs. M. BSA 1.89	*EH. MS. AF. IIC.	1.85	54	122	3.44	6.6	18.3	97	106/56, 75	31/16, 22	31/4	3475	1935	44
#535. 43 yrs. F. BSA 1.63	*EH. MS. AF. IIC.	2.19	80	121	4.74	5.5	17.1	96	92/57, 70	38/24, 29	38/1	2410	1355	44
#567. 35 yrs. M. BSA 1.71	*EH. MS. (T.I.) AF. IIC.	1.94	60	124	5.68	6.4	16.6	93	89/66, 75	54/29, 37	54/5	3338	1905	43
#642. 50 yrs. M. BSA 1.72	*EH. MS. AF. IIC.	2.23	60	123	4.52	5.5	19.1	94	113/74, 93	75/38, 50	75/4	2895	1410	51
#622. 36 yrs. M. BSA 1.61	*EH. MS. (T.I.)† (Graham-Steell) AF. IIC.	1.96	88	149	4.23	7.6	19.1	90	135/85, 102	105/49, 74	105/7	3496	1713	51
#618. 41 yrs. F. BSA 1.63	*EH. MS. (T.I.) AF. IIC.	2.61	80	138	6.24	5.3	15.8	95	125/78, 101	68/29, 46	68/8	3560	2095	41
#607. 35 yrs. F. BSA 1.48	*EH. MS. (T.I.)† (Graham-Steell) AF. IIIC.	2.07	85	130	5.70	6.3	17.9	95	114/80, 94	84/46, 60	84/3	2420	1340	45
#555. 29 yrs. F. BSA 1.86	EH. MS. (T.I.) AF. IIIC. Healed SBE.	1.42	91	122	5.24	8.6	16.2	96	104/70, 82	56/37, 44	56/11	4338	2402	44

⁂555. 20 yrs. F. BSA 1.86	EH. MS. (T.I.) AF. IIIC. Healed SBE.	1.42	91	122	5.24	8.6	16.2	96	104/70, 82	56/37, 44	56/11	4558	2402	44
	(c) Mitral stenosis and insufficiency with sinus rhythm													
⁂650. 27 yrs. M. BSA 1.86	EH. MS. MI. NSR. IA.	3.05	80	128	4.16	4.2	20.0	96	121/70, 85	15/5, 8	15/3	3370	1685	50
⁂564. 22 yrs. M. BSA 1.67	EH. MS. MI. SA. IA.	4.56	107	146	4.67	3.2	17.7	94	133/80, 101	23/11, 14	23/0	—	—	—
⁂606. 49 yrs. M. BSA 1.63	*EH. MS. MI. SA. IIC.	2.59	57	129	6.20	5.0	17.4	93	83/52, 63	38/17, 24	38/2	3650	1933	47
⁂559. 45 yrs. M. BSA 1.45	*EH. MS. MI. NSR. IIC.	2.92	80	111	4.13	3.8	18.6	97	109/70, 86	—	79/3	2680	1365	50
⁂612. 20 yrs. M. BSA 1.45	EH. MS. MI. (Graham-Steell) NST. IIC.	2.39	106	150	7.21	6.3	15.6	90	120/80, 100	79/42, 57	79/10	3404	1882	48
⁂538. 25 yrs. M. BSA 1.52	EH. MS. MI. SA. IIIC.	2.59	82	161	8.65	6.2	16.9	98	110/65, 81	42/21, 29	42/5	2920	1690	42
⁂518. 47 yrs. M. BSA 1.72	EH. MS. MI. NSR. IIIC.	3.09	93	145	5.70	4.7	15.9	94	120/79, 95	74/36, 52	74/10	3330	1830	45
	(d) Mitral stenosis and insufficiency with auricular fibrillation													
⁂641. 44 yrs. F. BSA 1.66	*EH. MS. MI. (T.I.) AF. VPC'S. IIC.	3.19	112	150	3.93	4.7	18.6	95	148/82, 103	33/16, 24	33/4	2400	1285	47
⁂387. 53 yrs. M. BSA 1.62	EH. MS. MI. (T.I.) AF. IIIC.	1.65	110	134	6.41	8.1	17.3	96	99/77, 87	—	43/11	—	—	—
⁂649. 42 yrs. M. BSA 2.01	*EH. MS. MI. (T.I.) AF. IIIC.	1.36	92	168	5.82	12.3	20.4	94	134/96, 112	96/53, 75	96/20	4478	2226	55
⁂206. 49 yrs. M. BSA 1.55	*EH. MS. MI. T.I. AF. IVD.	1.73	80	142	4.83	8.2	14.7	92	121/78, 88	—	96/17	4289	2743	36
⁂203, 64 yrs. F. BSA 1.52	*EH. MS. MI. T.I. †AF. IVE.	1.90	63	144	4.33	7.6	17.7	97	190/89, 125	—	117/22	5440	3370	43
	(e) Aortic insufficiency													
⁂498. 36 yrs. M. BSA 1.90	EH. AI. (Austin Flint) NSR. IA.	2.75	73	135	5.70	4.9	15.9	100	129/53, 84	16/8, 9	16/5	3530	2140	39

* Digitalized.

† Diagnosis confirmed by autopsy.

M^2BSA = per square meter of body surface area. AV diff. = arterio-venous oxygen difference. TBV = total blood volume. PV = plasma volume. H'crt = hematocrit. R.Q. = respiratory quotient. s = systolic. d = diastolic. m = mean.

EH = enlarged heart. MS = mitral stenosis.

MI = mitral insufficiency. AS = aortic stenosis. AI = aortic insufficiency. TS = tricuspid stenosis. TI = tricuspid insufficiency. BBB = bund'e branch block.

NSR = normal sinus rhythm. SA = sinus arrhythmia. NST = normal sinus tachycardia. VPC's = ventricular premature contractions. AF = auricular fibrillation. Healed SBE = healed subacute bacterial endocarditis.

TABLE 2.—*Physiologic Data in 13 Patients with Rheumatic Heart Disease and Multiple Valvular Lesions*

Case, Sex, Age BSA	Diagnosis	Cardiac Index (L./min./M² BSA)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	Ventilation (L/min./M² BSA)	AV diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg.			TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crt (%)
							cont. (vol.%)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle s/d			
#522. 17 yrs. M. BSA. 1.54	EH. MS. MI. AI. NSR. IA.	4.87	99	165	5.88	3.4	18.9	99	118/59, 80	16/6, 11	16/4	2520	1493	43
#637. 21 yrs. M. BSA. 1.79	EH. MS. MI. AI. NSR. IA.	2.86	78	141	4.94	4.9	18.9	98	144/55, 90	21/11, 15	21/4	2650	1430	46
#595. 28 yrs. M. BSA. 1.66	*EH. MS. AI. NSR. IIC.	2.32	68	119	4.44	5.1	19.2	96	113/68, 80	38/16, 24	38/4	2920	1470	50
#479. 33 yrs. M. BSA 1.70	*EH. MS. MI. AI. NSR. Incomplete AV Block IIC.	2.33	104	161	6.84	6.9	17.7	95	117/53, 82	—	—/3‡	3290	1805	45
#662. 26 yrs. F. BSA 1.51	*EH. MS. TS.§ NSR. IIC.	1.64	89	113	4.36	6.9	19.8	96	102/68, 83	46/27, 34	46/2	2917	1299	56
#359. 63 yrs. M. BSA 1.46	*EH. MS. MI. AI. NSR. IIC.	2.05	68	121	5.32	5.9	18.8	96	147/77, 106	41/14, 23	41/2	2730	1470	46
#459. 49 yrs. M. BSA 1.33	EH. MS. MI. AI. NSR. LBBB. IIIC.	1.60	94	155	7.40	9.7	17.5	93	144/60, 100	56/31, 39	56/3	2670	1465	45
#208. 48 yrs. M. BSA 1.50	*EH. MS. MI. AI. TI. AF. RBBB. IIIC.	1.70	56	138	5.90	8.1	16.7	96	†135/80, —	85/31, 48	85/10	—	—	—
#84. 58 yrs. M. BSA 1.70	*EH. MS. MI. AI. TI. AF. IVE.	1.95	79	158	6.49	8.1	15.3	98	140/78, 101	—	—/22‡	3870	2390	38
#180. 47 yrs. F. BSA 1.58	*EH. MS. MI. AS. AI. TI. AF. IVE.	1.21	97	138	6.54	11.4	19.8	92	163/72, 103	—	—/18‡	4140	2070	50
#87. 58 yrs. F. BSA 2.08	*EH. MS. MI. AS. AI. TI. AF. IVE.	2.65	92	186	4.28	7.0	17.6	90	230/95, 138	—	107/18	6220	3280	48
#80. 48 yrs. M. BSA 1.77	*EH. MS. MI. AS. TI. AF. IVE.	1.84	68	129	4.74	7.0	20.6	98	145/75, 102	—	—/17*	3690	1620	53
#495. 50 yrs. M. BSA 2.10	EH. MI. AI. TI. NSR. IVD.	2.79	80	151	4.68	5.4	12.2	94	139/64, 93	58/21, 35	58/15	4750	2950	38

* Digitalized.
† By sphygmomanometer.
‡ Right auricular mean pressure.
§ Confirmed by necropsy.

to control levels early in the recovery period. It is difficult in this patient to accept heterodynamism as the major mechanism for aggravation of the pulmonary hypertension; rather it is more likely that the increased pulmonary blood flow in the presence of minimal pulmonary stasis resulting from mitral stenosis produced the augmented pressures. Furthermore the increased flow suggests that the mitral block in this man was less severe than in the four individuals to be discussed below.

In contrast to the previous patient (case 552) none of the other four (cases 635, 567, 642, 622) who were asymptomatic at rest, had a normal rise in cardiac output (120 to 440 cc. increase in blood flow per 100 cc. increase in oxygen consumption) despite considerable variation in the severity of the exercise (increase in oxygen consumption ranged from 50 to 107 per cent, table 3). Pulmonary hypertension became more severe and was accompanied by a rise in right ventricular diastolic pressure and heart rate in all four of these patients, in whom, it should be noted, the resting cardiac outputs were all low and only one of whom (case 622) had a definite elevation of right ventricular diastolic pressure at rest. The early rapid increase in venous return to the right heart suggested to explain the reaction to exercise in case 591 is substantiated here by the rise in right ventricular end diastolic pressure in these patients. Three developed and maintained a plateau-like level of pulmonary artery pressures during exercise and in none was there an early decline in these pressures during recovery. It is impossible with these data to define the relative importance of mitral stenosis, left ventricular failure or pulmonary vascular disease in the enhancement of pulmonary hypertension in these patients.

Symptoms at Rest. Five patients of the 16 with mitral stenosis were dyspneic at rest when studied (cases 664, 633, 609, 607, 555). Two of these (cases 664, 607) had pulmonary rales alone, while a third (case 555) had in addition to rales, signs of right heart failure. Severe pulmonary hypertension was present in all. However, the cardiac output was normal in two, although very low in the other three.

The only patient with an elevated right ventricular diastolic pressure and blood volume was the one in right heart failure (case 555). Pulmonary hypertension was aggravated in the three individuals who were exercised (case 633, 609, 607, table 3), although in two (case 633, 609) there was no change in cardiac output and the third (case 607) had only a small increase (367 cc. per 100 cc. increase in oxygen consumption). The fixed cardiac output in two subjects, however, suggests the influence

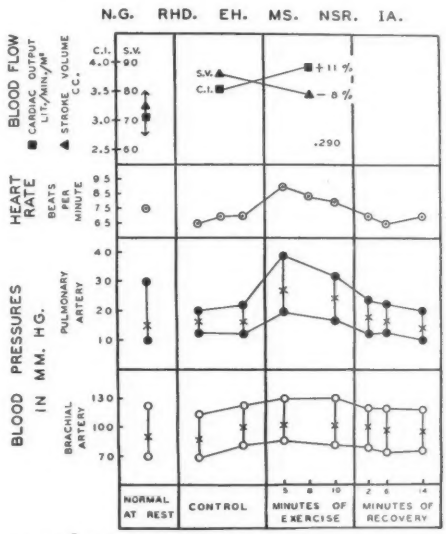

FIG. 2. The effect of exercise in a patient (case 591) with mitral stenosis and sinus rhythm who had normal hemodynamics at rest. Note the small rise in cardiac output and the fall in stroke volume accompanied by an increase in heart rate and the appearance of pulmonary hypertension. In this and other figures, normal values appear in the first or left-hand column. The value .290 which appears in the exercise column refers to the blood flow increase in liters per 100 cc. oxygen consumption increase.

of marked stenosis of the mitral valve or myocardial failure. As can be observed in figure 4, this exercise response produced pulsus alternans in the pulmonary artery tracing of one patient (case 609) which was not accompanied by alternation in the systemic artery. Pulsus alternans persisted throughout the recovery period and was noted in the right ventricular tracing after 10 minutes of recovery, at which time the end diastolic pressure was found to be elevated, and the pulmonary arterial pres-

† By sphygmomanometer.

TABLE 3.—*Physiologic Data Showing the Effect of Exercise in 15 Patients with Rheumatic Heart Disease*

Case	Time	Cardiac Index (L./min./M² BSA)	Stroke Volume (cc)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	R.Q.	AV diff. (vol. %)	Arterial Blood Oxygen			Pressures in mm. Hg		
								cont. (vol. %)	cap. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle d
#591	Rest	3.54	86	70	159	0.90	4.5	16.4	17.1	98	113/ 69, 89	20/13, 16	—
	Rest			71							122/ 80, 100	22/12, 16	—
	5 mins.*			88							130/ 86, 101	39/20, 27	—
	8 mins.	3.92	79	84	290	0.89	7.4	16.6	17.1	99			
	10 mins.			80							130/ 83, 101	32/17, 24	—
	0.5 mins.†			70							126/ 76, 96	31/15, 22	—
	2 mins.			70							120/ 79, 100	24/12, 18	—
	6 mins.			65							120/ 74, 97	23/12, 16	—
	11 mins.			70							120/ 75, 95	22/12, 17	—
	14 mins.			70							118/ 76, 95	20/10, 15	3
#552	Rest			70								30/13, 18	6
	Rest			60								31/14, 20	5
	Rest	2.33	69	60	128	0.84	5.5	17.4	18.2	98	122/ 75, 96	28/12, 18	6
	Rest			65							130/ 77, 102	29/13, 18	4
	Rest			65								31/14, 20	5
	Rest			60							123/ 71, 90	29/13, 19	5
	2 mins.*			100							163/ 99, 123	53/26, 35	15
	5 mins.	3.20	69	82	275	0.90	8.6	18.2	18.7	99			
	7 mins.			85							165/105, 130	49/25, 33	9
	1 mins.†			70							135/ 83, 105	31/14, 20	5
	2 mins.			60							138/ 82, 105	30/12, 18	4
	13 mins.			65							126/ 80, 98	28/11, 18	5
#635	Rest			61							106/ 56, 75	31/16, 22	4
	Rest	1.85	65	54	122	0.81	6.6	18.3	19.3	97	121/ 77, 94	30/15, 21	3
	Rest			60							132/ 81, 99	31/17, 22	3
	Rest	1.80	63	54	117	0.78	6.5	17.7	19.1	95	121/ 75, 91	28/16, 20	2
	4 mins.*			68								48/26, 34	6
	7 mins.			79								49/28, 35	6
	9 mins.	2.22	51	82	209	0.87	9.4	18.3	19.3	97			
	12 mins.			75							129/ 86, 103	49/28, 36	5
	2 mins.†			60							126/ 76, 113	34/18, 23	4
	15 mins.			60							129/ 75, 95	30/15, 20	3
	19 mins.			61							129/ 80, 98	31/16, 22	3
#567	Rest			65							89/ 66, 75	54/29, 37	5
	Rest	1.94	55	60	124	0.83	6.4	16.6	18.3	93	84/ 62, 71	53/23, 34	—
	Rest			60							93/ 66, 76	55/30, 37	5
	Rest	2.14	54	68	137	0.84	6.4	16.6	18.0	92	94/ 65, 77	55/26, 34	—
	Rest			60							98/ 67, 79	55/28, 36	—
	5 mins.*			75							105/ 73, 87	78/38, 51	10
	8 mins.	2.21	47	80	197	0.89	8.9	17.3	18.4	96			
	11 mins.			80							114/ 81, 94	81/43, 54	8
	2 mins.†			80							114/ 83, 97		6
	4 mins.			75								76/34, 46	—
	12 mins.			70							108/ 73, 97	58/27, 37	3

TABLE 3.—*Continued*

Case	Time	Cardiac Index (L./min./M² BSA)	Stroke Volume (cc)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	R.Q.	AV diff. (vol. %)	Arterial Blood Oxygen			Pressures in mm. Hg.		
								cont. (vol. %)	cap. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle d
#642	Rest	2.23	64	60	123	0.74	5.5	19.1	20.7	94	113/ 74, 93	75/38, 50	4
	Rest			52							116/ 70, 89	70/34, 47	5
	Rest	2.41	67	62	130	0.79	5.4	19.0	20.6	94	111/ 75, 89	76/40, 53	—
	Rest			71							106/ 71, 86	73/41, 54	—
	10 mins.*	2.86	47	104	363	0.96	12.7	19.9	21.2	96			
	12 mins.			120							115/ 80, 96	147/78, 106	10
	3 mins.†			70							101/ 75, 86	83/55, 65	9
	17 mins.			70							102/ 70, 84	63/39, 51	4
#622	Rest	1.96	36	88	149	0.77	7.6	19.1	21.6	90	145/ 97, 117	105/49, 74	7
	Rest	1.96	37	86	153	0.76	7.8	19.0	21.5	90	158/ 98, 118	105/48, 68	7
	Rest			85							135/ 85, 102	104/51, 72	5
	5 mins.*			110							138/ 91, 103	126/65, 89	12
	8 mins.			110							147/ 93, 108	135/69, 96	12
	11 mins.	2.06	37	122	244	0.81	11.8	19.4	21.6	91			
	13 mins.			110							152/ 91, 110	139/66, 97	11
	4 mins.†			87							157/103, 120	115/58, 81	6
	17 mins.			90							146/ 93, 110	105/52, 78	5
#633	Rest	3.19	56	100	166	0.74	5.2	15.5	18.8	84		83/42, 59	2
	Rest			100								79/42, 59	1
	Rest	3.23	56	102	159	0.76	4.9	15.1	18.8	82	106/ 63, 77	77/41, 57	2
	Rest			100								71/41 56	1
	Rest			107							92/ 58, 70	70/38, 55	1
	4 mins.*			107							113/ 69, 83	89/48, 66	4
	7 mins.			107							100/ 67, 78	89/45, 61	4
	9 mins.	3.13	50	110	197	0.80	6.3	15.0	18.3	84			
	11 mins.			107							106, 66, 79	90/48, 64	5
	2 mins.†			103							98/ 54, 67	81/42, 59	1
	16 mins.			107							99/ 64, 75	70/41, 57	0
	19 mins.			110							87/ 61, 67	68/38, 58	0
#609	Rest	1.83	29	100	135	0.86	7.4	15.8	17.3	94	95/ 69, 80	108/59, 81	—
	Rest	1.66	26	100	131	0.86	7.9	15.6	17.3	93	98/ 68, 85	117/61, 87	—
	3 mins.*			150							95/ 60, 75	140/75, 101	—
	6 mins.	1.73	19	142	239	0.99	13.8	17.5	19.2	93			
	8 mins.			136							105/ 72, 85	151/83, 108	—
	0.25 mins.†			136							108/ 75, 84	158/88, 101	—
	2 mins.			111							109/ 76, 86	143/75, 104	—
	10 mins.			104							104/ 75, 82	123/69, 94	8

TABLE 3.—*Continued*

Case	Time	Cardiac Index (L./min./M² BSA)	Stroke Volume (cc)	Heart Rate (beats/min.)	Oxygen Consumption (cc./min./M² BSA)	R.Q.	AV diff. (vol. %)	Arterial Blood Oxygen			Pressures in mm. Hg		
								cont. (vol. %)	cap. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle d
*607	Rest	2.07	36	85	130	0.91	6.3	17.9	19.1	95	114/ 80, 94	84/46, 60	3
	Rest	2.15	38	84	135	0.92	6.3	17.8	19.3	95	109/ 74, 86	90/43, 65	—
	5 mins.*			130							130/ 84, 99	122/62, 85	14
	7 mins.	2.46	30	120	226	0.88	9.2	17.4	19.6	91			
	10 mins.			110							131/ 88, 97	127/62, 85	9
	1 mins.†			90							132/ 85, 97	120/54, 80	—
	6 mins.			100							122/ 81, 90	95/48, 65	—
	9 mins.			90							124/ 85, 97	88/46, 67	4
*650	Rest			80							121/ 70, 85	15/ 5, 8	3
	Rest			75								14/ 5, 10	2
	Rest			78								17/ 7, 11	3
	Rest	3.05	71	80	128	0.82	4.2	20.0	21.1	96		14/ 6, 9	1
	Rest			78								15/ 6, 10	2
	Rest			78								14/ 4, 8	1
	4 mins.*			83							152/ 82, 104	20/ 9, 15	5
	6 mins.			85								22/ 8, 14	5
	7 mins.			88								18/ 7, 11	4
	10 mins.	4.36	88	92	296	0.82	6.8	20.4	21.3	98			
	12 mins.			90								18/ 8, 13	3
	13 mins.			88								18/ 7, 12	3
	14 mins.			85							148/ 80, 100	17/ 7, 13	3
	2 mins.†			77								16/ 7, 10	1
	4 mins.			80							132/ 76, 93	15/ 6, 9	3
	11 mins.			80							135/ 77, 97	15/ 6, 10	2
*606	Rest			55							83/ 52, 63	38/17, 24	—
	Rest	2.26	66	56	125	0.87	5.5	17.6	19.1	94	93/ 56, 71	39/16, 24	2
	Rest	2.59	74	57	129	0.80	5.0	17.4	19.2	93	103/ 65, 81	38/16, 22	1
	9 mins.*			85								88/39, 58	—
	11 mins.			78							116/ 71, 88	85/42, 60	—
	14 mins.	2.92	53	90	242	0.90	8.5	18.6	20.3	93			
	20 mins.			78							116/ 71, 83	74/32, 48	4
	23 mins.			75							109/ 64, 84	75/33, 44	4
	2 mins.†			70							110/ 69, 86	59/25, 38	2
	21 mins.			65							105/ 67, 83	38/16, 27	1
	23 mins.			62							100/ 62, 79	40/16, 24	2
*538	Rest			60								39/16, 26	—
	Rest	2.62	73	57	134	0.76	5.1	15.6	16.1	99	116/ 57, 75	37/14, 24	—
	Rest			52							124/ 64, 83	36/15, 24	—
	Rest	2.49	70	56	134	0.68	5.4	14.9	15.8	97	133/ 69, 90	36/16, 24	—
	5 mins.*			107							138/ 79, 101	77/34, 52	—
	8 mins.			100							132/ 78, 93	76/32, 48	—
	9 mins.	3.50	53	104	308	0.85	8.8	15.7	16.4	98			
	10 mins.			115							131/ 78, 94	76/38, 53	—
	5 mins.†			50							114/ 65, 83	37/14, 20	2

TABLE 3.—*Continued*

Case	Time	Cardiac Index (L/ min./ M² BSA)	Stroke Volume (cc)	Heart Rate (beats/ min.)	Oxygen Consumption (cc/ min./ M² BSA)	R.Q.	AV diff. (vol. %)	Arterial Blood Oxygen			Pressures in mm. Hg		
								cont. (vol. %)	cap. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle d
#637	Rest			75								21/11, 15	4
	Rest	2.86	66	78	141	0.89	4.9	18.9	19.7	98	144/ 55, 90	22/ 9, 15	5
	Rest	2.74	63	78	137	0.91	5.0	19.0	19.9	97		20/ 7, 13	4
	Rest			73							124/ 55, 81	19/ 7, 13	3
	4 mins.*			90							160/ 78, 106	40/19, 27	9
	8 mins.			91							163/ 78, 112	36/18, 25	5
	10 mins.	4.52	84	96	316	0.90	7.0	18.9	20.6	98			
	11 mins.			91							171/ 82, 119	31/13, 20	4
	4 mins.†			80							154/ 72, 103	20/ 7, 11	2
	18 mins.			75							144/ 59, 90	21/ 9, 13	3
#595	Rest	2.32	57	68	119	0.85	5.1	19.2	20.4	96	113/ 68, 80	38/16, 24	4
	Rest	2.50	61	68	127	0.81	5.1	19.1	20.6	96	113/ 62, 80	34/17, 24	5
	Rest			62							108/ 60, 80	37/15, 22	6
	2 mins.*			88							119/ 63, 85	59/31, 43	9
	5 mins.			83							119/ 64, 85	59/29, 42	8
	10 mins.	3.16	61	86	237	0.92	7.5	20.1	20.9	98			
	13 mins.			88							130/ 69, 92	61/31, 44	9
	15 mins.			88							130/ 68, 93	59/32, 45	—
	4 mins.†			75							118/ 63, 88	44/19, 30	4
	9 mins.			65							117/ 62, 86	38/15, 23	5
	23 mins.			60							115/ 62, 84	34/13, 20	5
#662	Rest	1.64	28	89	113	0.85	6.9	19.8	21.0	96	102/ 68, 83	46/27, 34	2
	Rest										105/ 69, 87	44/26, 33	2
	Rest	1.77	30	89	117	0.86	6.6	19.6	21.2	94	107/ 68, 86	45/28, 32	2
	4 mins.*			98							116/ 76, 93	58/33, 42	1
	9 mins.	1.87	28	100	223	0.92	11.9	20.2	22.1	93			
	11 mins.			100							121/ 78, 97	62/34, 42	1
	14 mins.			97							120/ 78, 97	67/35, 46	1
	5 mins.†			94							112/ 69, 89	49/25, 33	—
	13 mins.			88							103/ 60, 77	41/22, 28	0

* Minutes of exercise

† Minutes after cessation of exercise.

sures had not reached resting levels. This would undoubtedly appear to be a manifestation of sustained right ventricular strain.

The response to acute digitalization was observed in the patient who was in frank right heart failure with dyspnea and orthopnea when first studied (case 555). After the control observations were made at rest, this patient received intravenous Digoxin. As can be seen in figure 5, table 4, the typical response of the failing heart to digitalization appeared, as the cardiac output and stroke volume rose, 49 per cent and 110 per cent respectively. The pulmonary arterial and right ventricular diastolic pressures declined sharply as both ventricles emptied more efficiently, but the systolic pres-

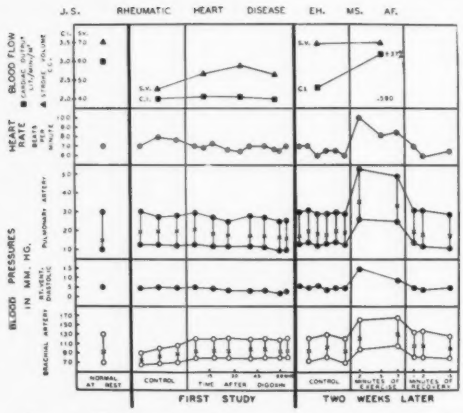

FIG. 3. Two studies in a patient (case 552) with mitral stenosis and auricular fibrillation. The patient received intravenous Digoxin at the time of the first study. Two weeks later, at the time of the second catheterization, the response to exercise was determined. (For discussion see text.)

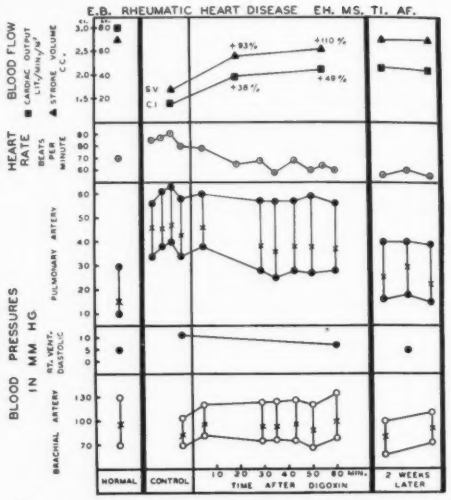

FIG. 5. Two studies in a patient (case 555) with mitral stenosis, tricuspid insufficiency and auricular fibrillation. The acute response to Digoxin is seen in the first study, while the second series of measurements were made two weeks later. (For discussion see text.)

sures did not change in the first hour post Digoxin. The fixation of the systolic pressures was probably the result of increased pulmonary blood flow in face of increased pulmonary vascular resistance due either to mitral stenosis or pulmonary vascular sclerosis or both. It seems unlikely that the fall in pulmonary artery diastolic pressure could be explained only by the fall in heart rate and resulting prolongation of the left heart filling time, in view of the marked increase in pulmonary blood flow; rather it must be ascribed to better left ventricular emptying. Two weeks later, after an interval of careful cardiac regimen and maintenance Digoxin, the patient was symptom

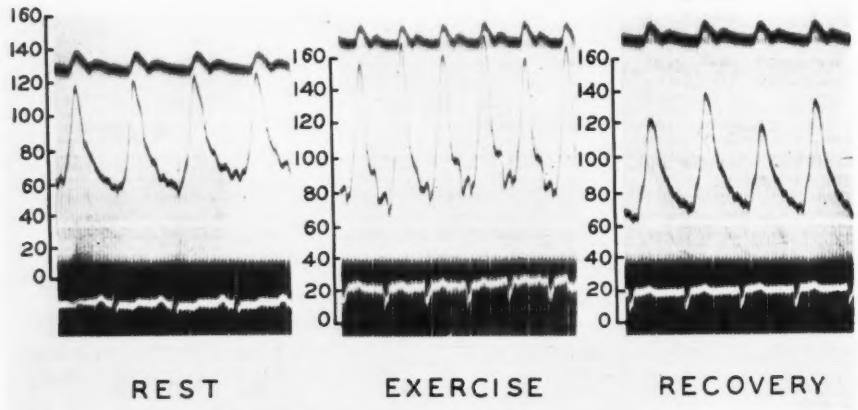

FIG. 4. Pressure tracings illustrating the appearance of pulsus alternans in the pulmonary artery during and after exercise in a patient (case 609) with mitral stenosis and sinus rhythm. The calibration scale refers to the curve of the pulmonary artery which is the lower pressure tracing. The upper tracing is from the brachial artery. Lead II was recorded at rest and lead aV_R was used during exercise and recovery.

free. The second hemodynamic study (fig. 5, table 5) revealed that the improved level of cardiac output and stroke volume credited to less, tricuspid insufficiency persisted as demonstrated by the right auricular pressure tracings. The further fall in pulmonary pressures can

TABLE 4.—*Effect of Digoxin in Four Patients with Rheumatic Heart Disease*

Case	Time	Cardiac Index (L/min./ N² BSA)	Heart Rate (beats/ min.)	Oxygen Consumption (cc/ min./M² BSA)	R.Q.	A-V Oxygen Diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg.		
							cont. (vols. %)	sat. (%)	Brachial Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle d
*555	Control	1.42	91	122	0.98	8.6	16.2	96	104/70, 82	56/37, 44	11
	55*	2.11	64	122	0.93	5.8	15.7	95	135/79, 97	55/28, 37	7
*612	Control	2.39	106	150	0.84	6.3	15.6	90	120/80, 100	79/42, 57	10
	50†	2.82	89	163	0.84	5.8	15.4	89	125/78, 88	66/31, 46	4
*538	Control	2.59	82	161	0.89	6.2	16.9	98	110/65, 81	42/21, 29	5
	65*	3.18	67	153	0.86	4.8	15.9	96	128/70, 88	43/16, 24	2
*518	Control	3.09	93	145	0.89	4.7	15.9	94	120/79, 95	74/36, 52	10
	62†	3.63	88	152	0.83	4.2	15.3	94	111/63, 81	64/31, 45	6

* Minutes after start of injection of 1.25 mg. Digoxin.
† Minutes after start of injection of 1.00 mg. Digoxin.

TABLE 5.—*Serial Hemodynamic Measurements at Rest in Five Patients with Rheumatic Heart Disease*

Case	BSA	Cardiac Index (L/ min./ M² BSA)	Stroke Volume (cc)	Heart Rate (beats/min.)	Oxygen Consumption (cc/ min./ M² BSA)	R.Q.	AV diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg			TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crt (%)
								cont. (vol. %)	sat. (%)	Systemic Artery s/d, m	Pulmonary Artery s/d, m	Right Ventricle s/d			
*552(a)	1.77	2.00	45	79	108	0.90	5.4	17.6	95	105/75, 89	28/12, 19	28/4	3310	1755	47
*(b)	1.78	2.33	69	60	128	0.84	5.5	17.4	98	123/71, 90	29/13, 19	29/5	3350	1880	44
*555(a)	1.86	1.42	29	91	122	0.98	8.6	16.2	96	104/70, 82	56/37, 44	56/11	4338	2402	44
*(b)	1.83	2.15	70	60	108	0.93	5.0	14.9	92	100/59, 81	40/16, 25	40/5	3750	2294	41
*538(a)	1.52	2.59	48	82	161	0.89	6.2	16.9	98	110/65, 81	42/21, 29	42/5	2920	1690	42
†(b)	1.58	2.62	73	57	134	0.76	5.1	15.6	99	124/64, 83	36/15, 24	—	3036	1868	39
*649(a)	2.01	1.36	30	92	168	0.76	12.3	20.4	94	134/96, 112	96/53, 75	96/20	4478	2226	55
‡(b)	1.97	1.55	36	84	149	0.81	9.6	20.1	94	127/84, 103	85/45, 59	85/9	4380	2053	53
*87 (a)	2.08	2.65	60	92	186	0.72	7.0	17.6	90	230/95, 138	—	107/18	6220	3280	48
‡(b)	1.77	3.86	83	82	189	0.68	4.9	20.1	94	165/61, 98	—	59/7	4270	2220	48

* A two-week interval separates studies (a) and (b).
† A four-month interval separates studies (a) and (b).
‡ A one-month interval separates studies (a) and (b).

an acute Digoxin effect had been maintained. There was, however, a striking decline in all phases of pulmonary artery pressures, the blood volume was lower, and the right ventricular diastolic level was normal. Nonetheless, tricuspid insufficiency persisted as demonstrated by the right auricular pressure tracings. The further fall in pulmonary pressures can be ascribed to mobilization of blood out of the lungs probably arrived at by improvement in the function of the left ventricle or by reduction in total blood volume or by their interrelated effects. The sequence of changes thus

does not imply any alteration in the degree of mitral stenosis or pulmonary arteriolar sclerosis. These studies therefore indicate that in addition to right heart failure, left heart failure was present and contributed in part to pulmonary hypertension.

In summary no single hemodynamic pattern at rest emerges in these patients with mitral stenosis, that is, the level of cardiac output and of lesser circulation pressures showed considerable variation. The response to exercise, on the other hand, uncovered one consistency,

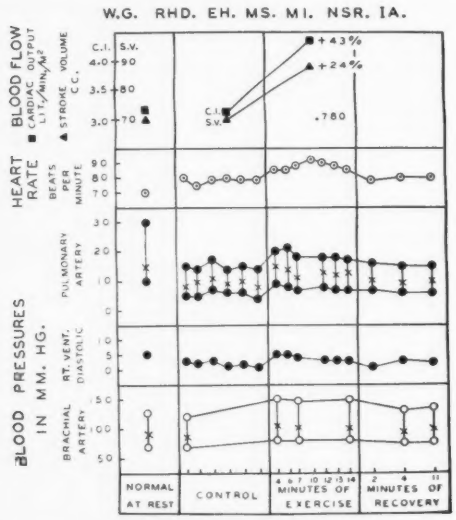

FIG. 6. The effect of exercise in a patient (case 650) with mitral stenosis and insufficiency and sinus rhythm. The exercise response was completely normal. Note the absence of pulmonary hypertension before and during exercise.

pre-existing pulmonary hypertension was always aggravated even in the absence of an increase in blood flow. The nature of pulmonary hypertension was defined by Digoxin studies and subsequent serial measurements in two patients and found to be due in one instance to left ventricular failure and in the other to mechanical block at the mitral valve.

Mitral Stenosis and Insufficiency

Seven of this group had sinus rhythm and the remaining five auricular fibrillation (groups c and d, table 1). Six of this group had no evidence of left ventricular enlargement. As in the patients with uncomplicated mitral stenosis the results will be discussed in relation to symptomatology.

No Symptoms. Two of this group of 12 had never had any evidence of a diminished cardiac reserve (cases 650 and 564) and displayed essentially normal hemodynamics at rest. Furthermore, one of these (case 650, table 3) behaved as a normal individual in response to moderate exercise. As can be seen in figure 6, with an increased stroke volume and a 43 per cent rise in cardiac output, which represents an increase in blood flow of 780 cc. per 100 cc. increase in oxygen consumption, there was no pulmonary hypertension or significant elevation of right ventricular pressures. The findings in this man demonstrate a most important fact, namely that the mere presence of a mitral valvular deformity does not imply altered hemodynamics within this range of exercise.

Symptoms on Exertion. Three of the patients with mitral stenosis and insufficiency were more or less incapacitated by exertional dyspnea but were asymptomatic at rest and free of signs of cardiac insufficiency at the time of study (cases 606, 559, 641). Just as in the patients with mitral stenosis alone who fell into this symptomatic group, there was a fairly consistent hemodynamic pattern. Pulmonary hypertension varied from mild to severe and the cardiac output was either normal or slightly reduced. The right ventricular diastolic pressure was normal in all at rest and in only one (case 606) was the plasma volume increased. In order to investigate the response to stress in this type of patient one of the group (case 606, table 3) was exercised. He showed an abnormal response characterized by a small rise in cardiac output (405 cc. per 100 cc. increase in oxygen consumption), a fall in stroke volume, an increase in heart rate and the appearance of severe pulmonary hypertension when the latter had been only moderate at rest.

Symptoms at Rest. Dyspnea at rest with signs of pulmonary congestion and evidence of right heart failure were present in six subjects with mitral stenosis and insufficiency at the time of cardiac catheterization (cases 538, 518, 387,

649, 206, 203). An additional patient (case 612) denied dyspnea at rest but had convincing evidence of pulmonary as well as of peripheral congestion. In these seven subjects moderate to severe pulmonary hypertension accompanied an elevation of the right ventricular diastolic pressure which in all but one (case 538) was above 10 mm. Hg. Systemic blood flow was reduced in all but one subject (case 518), and with but a single exception (case 538) significant hypervolemia was present.

The acute response to intravenous Digoxin was observed in three of these patients with congestive failure (table 4). In two of them (cases 612 and 518) a rise in cardiac output was accompanied by a fall in all the lesser circuit pressures, pointing to the fact that there was an element of left as well as of right failure present. The reaction of the third (case 538) was similar to that of the patient pictured in figure 5, that is, the pulmonary artery systolic level remained unchanged while there was a fall in pulmonary artery diastolic and mean pressures, as well as in right ventricular diastolic pressure, associated with the rise in cardiac output. It is interesting that in this patient the right ventricular diastolic pressure was at the upper limit of normal prior to the administration of the glycoside, but fell thereafter—which suggests that although the absolute level of this pressure was within normal range, it actually represented an element of right heart failure in this patient. This young man was subsequently discharged symptom free. Three months later he was readmitted in cardiac failure and with evidence of digitalis toxicity. After one month in the hospital he was again free of evidence of heart failure, at which time he was restudied (table 5). Essentially the same degree of pulmonary hypertension existed as was found at the end of the Digoxin study, and the blood volume, normal on the first study, was unaltered. The increase in cardiac output however, had not been maintained, the systemic blood flow being at the same level as before digitalization. It was at this time, namely, when there was no clinical evidence of failure, that the patient was exercised. The exertion evoked a 37 per cent rise in cardiac output with the appearance of severe and sustained pulmonary hypertension (table 3). The increase in cardiac output was probably slightly less than normal (504 cc. per 100 cc. increase in oxygen consumption). These latter studies do not definitely distinguish between three possible causes for the remaining pulmonary hypertension—mitral stenosis, pulmonary vascular disease, or left heart failure—in this young man who had been found to have cardiac failure a few months before. At a considerably later date the patient was found at operation to have a marked mitral stenosis with some insufficiency.

In one patient serial measurements before and after an intensified medical regime (case 649, table 5) were made in order to clarify if possible the nature of his pulmonary hypertension. This man had had increasing failure despite full digitalization. First studied in right heart failure with dyspnea and orthopnea, he had severe pulmonary hypertension, a markedly elevated end diastolic pressure in the right ventricle and a very low cardiac output and stroke volume. For the next month in the hospital, a regime was followed which consisted of frequent mercurial diuretics, salt poor diet, strict bed rest as well as continued digitalis. At the time of the second catheterization the patient was improved, the most striking physical finding being a reduction in size of the previously markedly enlarged and tender liver. The study revealed only a mild decrease in pulmonary hypertension and a slight increase in cardiac output and stroke volume. The most marked change was the decline of the extremely high right ventricular diastolic pressure to a much lower level. However, tricuspid insufficiency was still present and the large blood volume was unchanged. Apparently the medical regime had little effect on the pulmonary hypertension, suggesting either mitral stenosis with pulmonary vascular sclerosis or intractable left ventricular failure. The striking benefit of this month of therapy was the improved performance of the right ventricle.

In summary, these patients with both stenosis and insufficiency of the mitral valve resembled those with mitral stenosis alone. The same qualitative and quantitative variations were present in both groups at rest and during

exercise. In this group with stenosis and insufficiency left ventricular failure was also demonstrated to be in part responsible for pulmonary hypertension in some patients. It therefore appears that with the methods used the effects of mitral stenosis alone on pressure and flow could not be distinguished from those ascribed to mitral insufficiency and stenosis.

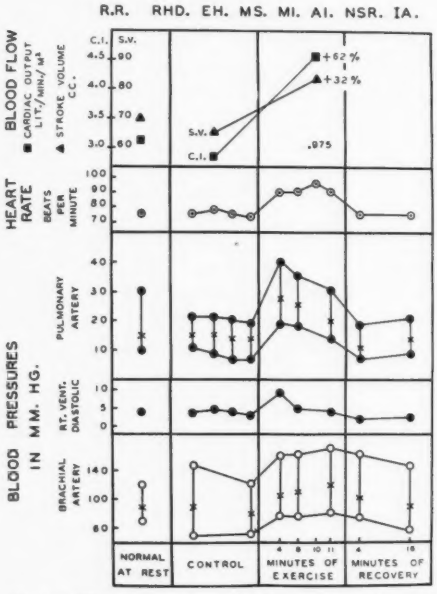

FIG. 7. The effect of exercise in a patient (case 637) with mitral stenosis and insufficiency, aortic insufficiency and sinus rhythm. Note the normal rise in cardiac output and stroke volume during exercise accompanied by the appearance of pulmonary hypertension and an elevated right ventricular diastolic pressure. The percentage increase in cardiac output during exercise in this patient, and all others where duplicate control determinations were made, was calculated using an average of the two control values.

Multiple Valvular Lesions

So far the material has included the circulatory effects of a single valvular deformity, mitral stenosis with or without insufficiency. Before considering the changes produced by involvement of more than one valve, it might be helpful to state briefly the hemodynamic findings in one patient with only aortic insufficiency (case 498) who was free of cardiac symptoms, but was admitted for acute and chronic alcoholism. All measurements (table 1) were within normal limits except for a slightly increased plasma volume. No studies were conducted during exercise.

The 13 cases who were considered to have more than one valve involved by the rheumatic process (table 2) can also be subdivided into three groups on the basis of symptoms. Eight had sinus rhythm and the remainder auricular fibrillation. It should be noted that only 1 of the 12 subjects with aortic valvular lesions had no evidence of left ventricular enlargement (case 595).

No Symptoms. Two patients were completely asymptomatic (cases 522 and 637) and had essentially normal hemodynamic findings at rest. One of these (case 637) was exercised. As can be seen in table 3 and figure 7, there was a normal rise in cardiac output, stroke volume and heart rate (an increase in blood flow of 975 cc. per 100 cc. increase in oxygen consumption), but this was accompanied by a sharp rise in pulmonary artery and right ventricular pressures to abnormal levels. However, the pressure rise was not sustained and although exercise remained at a steady pace the end diastolic ventricular pressure returned to normal and the pulmonary pressures decreased considerably during this period. The performance during exercise in this man could be ascribed to the effect of mitral stenosis and be explained in the same manner as in a previous patient (case 552). On the other hand in the presence of aortic insufficiency and an enlarged left ventricle temporary left ventricular failure early in exercise could be postulated. The early increased venous return to the right heart, effecting an increased pulmonary blood flow, was transferred to the abnormal left ventricle which, however, could not eject this added volume. The resulting increased diastolic residual volume caused a rise in pressure in the left ventricle and throughout the lesser circuit resulting in pulmonary hypertension. The resolution of this pulmonary hypertension later in exercise might be explained by an improvement in function of the left ventricle due either to (a) intrinsic improvement in ventricular ejection, (b) systemic vasodilatation, or (c) a relative diminution in systemic venous return

and thereby a relative reduction in right ventricular output and left ventricular inflow. The over-all effect would be a reduction in pulmonary blood volume and hence in pulmonary artery pressures.

Symptoms on Exertion. Four patients (cases 595, 479, 662, 359), asymptomatic at rest, were free of evidence of right heart failure and pulmonary rales when studied. Moderate pulmonary hypertension accompanied a considerably reduced systemic blood flow. In all, the right ventricular diastolic pressure and blood volume were within the normal range. Two of these subjects were exercised (cases 595 and 662, table 3) and both developed and maintained the same degree of pulmonary hypertension. In one (case 595) this was effected with a normal increase in cardiac output (an increase of 658 cc. of blood flow per 100 cc. increase in oxygen consumption) although it should be noted that the actual level of blood flow achieved during exercise was not normal. In the other patient blood flow did not rise significantly. The absence of a rise in right ventricular diastolic pressure in the latter patient (case 662) was undoubtedly related to her tricuspid stenosis, that is, the increased venous return was trapped in the right auricle and hence much of it did not reach the right ventricle. In this instance, therefore, the rise in pulmonary artery pressure could be ascribed only to the rise in heart rate.

One of the other patients was further explored in a different manner (case 359). When fully digitalized he was given oral quinidine and was found to have a fall in systemic blood pressure, a rise in cardiac output and a diminution in his pulmonary artery pressures, changes which indicated that left ventricular failure rather than mitral stenosis was the cause of pulmonary hypertension.[13]

Symptoms at Rest. Six of the last seven patients in this group with multiple valvular lesions were in profound congestive failure when examined (cases 208, 84, 180, 87, 80, 495). The seventh (case 459) although dyspneic at rest had neither pulmonary rales nor evidence of right heart failure. Cardiac output was low in all but one (case 495) and severe pulmonary hypertension was present in all in whom it was measured or in whom this could be inferred from the height of the right ventricular systolic pressures. All but one (case 459) had elevation of the right ventricular diastolic or right auricular mean pressures and an increased blood volume. None of these subjects was exercised but two were further examined. Abolition of pulmonary hypertension in one by acute digitalization (case 459) demonstrated the presence of left ventricular failure.[13] The other patient (case 87) also had an element of left ventricular as well as of right ventricular failure as revealed by serial studies (table 5). Following the first study at which time she was in profound failure, as she had been for many months, she was placed on an intensive cardiac regime for four weeks. Clinical improvement at the time of the second study was paralleled by physiologic observations of improved circulatory function. An increased cardiac output and stroke volume were accompanied by a marked decline in right heart pressures and blood volume.

In summary, no characteristic could be defined at rest, during exercise, or from Digoxin studies, in these patients with multiple valvular lesions to distinguish them from subjects with mitral valvular disease only.

In the previous consideration of the hemodynamic changes in relation to valvular deformities and clinical complaints one symptom, *hemoptysis*, was not commented upon. Although 11 of the 42 patients gave a history of blood spitting, in only seven of these did the episodes occur in the recent past (cases 633, 567, 642, 650, 518, 595, 479). In the six subjects with recent hemoptyses and pulmonary artery pressure measurements, one (case 650) had normal hemodynamics, one (case 595) had moderate elevation in pulmonary artery pressures and the remaining four had severe pulmonary hypertension. It should be recalled, however, that 12 other patients with severe pulmonary hypertension did not have any history of bleeding. It would therefore appear that hemoptysis is governed by mechanisms which are not directly assessed by measurements of pulmonary artery pressures.

In any evaluation of the cardiac patient, considerable stress is always placed upon *heart*

size. Obviously many factors operate to alter cardiac dimensions, perhaps one of the most important being the relationship between myocardial function and diastolic residual volume. Unfortunately, reliable technics are not yet available for measurement of the latter. Nonetheless, it seems worthwhile to call attention to the fact that heart size as demonstrated by x-ray varied considerably in these patients and could not be related to the level of pulmonary artery pressures. For example, a patient with mild pulmonary hypertension (case 552) showed considerable cardiac enlargement (fig. 8*a*) while in another case (case 609) whose pulmonary artery pressures were so high that at rest as well as on exercise they exceeded those of the brachial artery, the heart was much smaller (fig. 8*b*).

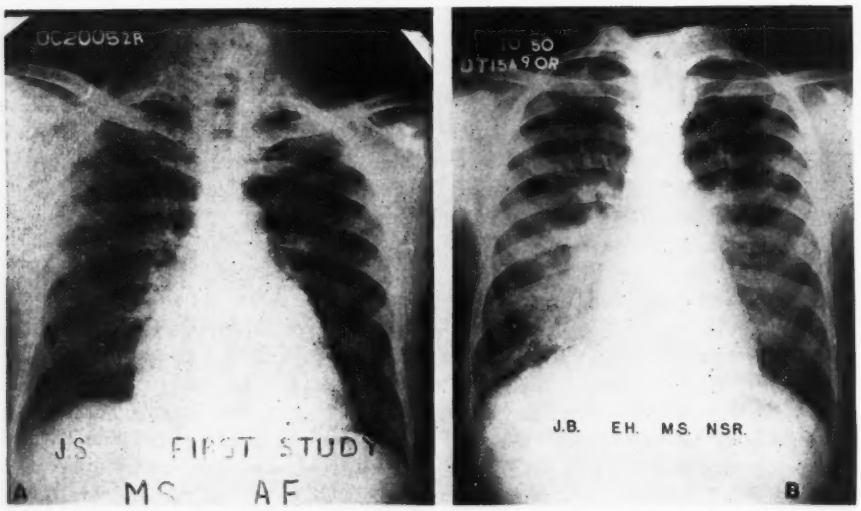

FIG. 8. (*A*) Roentgenogram of patient 552. (*B*) Roentgenogram of patient 609. For discussion see text.

Functional Valvular Lesions

In these 42 patients with rheumatic heart disease, functional incompetence of two valves was encountered. Four subjects were considered to have pulmonic incompetence and a Graham-Steell murmur inasmuch as there was no enlargement of the left ventricle and no confirmatory signs of aortic incompetence. Two of these came to postmortem examination and no aortic insufficiency was demonstrated. All four had severe pulmonary hypertension but there was no characteristic form to the pulmonary artery pressure curve, nor was the pulse pressure unusually wide. Eight other subjects had no evidence of this murmur despite levels of pressure higher than some of those individuals with the murmur of pulmonic incompetence.

Tricuspid insufficiency, as proved by right auricular pressure curves, complicated cardiac function in 16 of these 42 cases. When the clinical picture characteristic of tricuspid insufficiency was present (indicated in tables 1, 2 by unbracketed *T. I.*) the right auricular mean and right ventricular diastolic pressures were elevated as might be expected. However, physiologic evidence of this lesion was found in patients in whom there was no manifestation of it clinically and in whom there was neither clinical nor physiologic indication of right heart failure, that is, there was no hepatomegaly, edema, prominence of jugular pulsations or elevation of the right auricular mean or ventricular diastolic pressure above 5 mm. Hg (cases 567, 607, 641).

Auricular fibrillation was the basic mechanism in all but one of these 16 patients. This association may have been related to the advanced stage of rheumatic heart disease in

these patients and hence be merely coincidental, the insufficiency resulting from a markedly dilated valve ring accompanying cardiac failure with or without scarification of the valve leaflets. On the other hand, the arrhythmia may have had a dynamic relationship to the valve incompetence and predisposed to in-

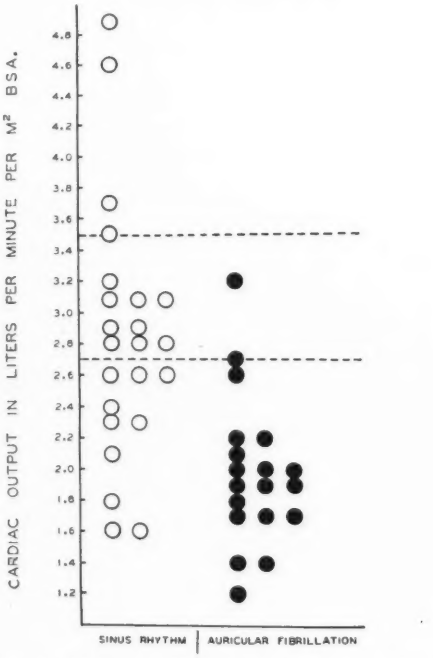

FIG. 9. Graph illustrating the level of resting cardiac output in 23 patients with sinus rhythm as compared with the cardiac output of 19 patients with auricular fibrillation. Each open circle represents one subject with sinus rhythm and each solid circle one with auricular fibrillation. The broken horizontal lines bracket the range of normal resting cardiac output. Note that 17 of the 19 patients with auricular fibrillation have a low cardiac output as compared with 10 of 23 with sinus rhythm.

sufficiency because of the poor valve closure which obtained when there was no auricular systole preceding ventricular systole. The latter concept is reinforced by the fact that of the 19 patients in the entire group who had auricular fibrillation, 16 had right auricular pressure curves which could be satisfactorily analyzed for fine detail; all but one of these 16 had evidence of tricuspid insufficiency. In patients with auricular fibrillation there was another consistent finding in addition to the high incidence of tricuspid insufficiency. In general they had a lower cardiac output than did subjects with sinus rhythm (fig. 9). It should be recalled however that all of the subjects with auricular fibrillation had had at least one episode of cardiac failure and hence were in a more advanced stage of rheumatic heart disease than those with a sinus rhythm. However, if one considers just the patients with mitral stenosis alone one finds that in the seven with sinus rhythm the cardiac index averaged 2.97 liters per minute per square meter B.S.A., while in nine with auricular fibrillation the average value was 2.03, although heart rate and pulmonary artery pressures were much the same in the two groups.

COMMENTS

When the studies on the dynamics of the circulation in rheumatic heart disease were first started a number of years ago[1] patients examined were in the main those in the advanced stage of the disease, where the picture of chronic congestive failure predominated. It soon became apparent that the circulatory abnormalities found, namely a low cardiac output and high pulmonary artery, right ventricular and auricular pressures were not specific to rheumatic heart disease, but marked the advanced stage of other forms of heart disease in chronic failure. Patients with hypertensive and arteriosclerotic heart disease, even some forms of chronic cor pulmonale could not be distinguished hemodynamically once chronic congestive failure had developed. This fact prompted the study of the early stages, and whenever possible the asymptomatic phase, of rheumatic heart disease in an attempt to chart the natural history of the disease from a hemodynamic standpoint and to elucidate the mechanisms whereby these alterations occurred. It is important to remember that the studies here presented were made in those subjects where all possible clinical means had been employed to rule out rheumatic activity. Hence, in the majority, the changes found are the sequelae of the disease which was considered to be in an inactive form.

In this entire group of 42 patients symptomatology proved to be a better indication of hemodynamic findings than did the anatomic valvular lesions. This is not surprising since symptoms afford a better estimate of the patients' over-all performance, taking into account not only all degrees of mechanical deformity present but also variations in myocardial function. In a review of the groups symptomatically it has been clearly shown that the dynamics at rest were normal in the asymptomatic subjects but the response to exercise was variable and occasionally abnormal. The appearance of pulmonary hypertension on exertion in the asymptomatic subject serves to illustrate the point that circulatory stress may exist under certain conditions and may be impossible to detect clinically without the aid of the more refined examinations here employed.

In the group of patients who were symptomatic on exertion, pulmonary hypertension was a consistent finding at rest, which suggests that left ventricular failure (or strain) was present, or that a more severe degree of valvular deformity existed than in the previous group, or that changes had taken place in the pulmonary vascular bed. The level of cardiac output on the other hand, was variable which undoubtedly is a reflection of the interaction of the numerous factors which control blood flow, for example, valvular competence, myocardial function and heart rate. Exercise was performed at the price of further circulatory embarrassment in all these patients. Of particular interest was the finding of an elevated right ventricular end diastolic pressure on exertion, when at rest it had been normal. This certainly suggests that the right heart was operating under strain. When an elevated end diastolic pressure was encountered at rest in the absence of the clinical signs of congestive right heart failure, one suspects that clinically occult cardiac failure or at least a more severe degree of strain was present than in the patients who developed an elevation of this pressure only on exercise. At these two stages of right heart performance it may still be possible for the patient to show some increase in cardiac output, although it is obvious that the myocardial fibers are nearing the point of overstretch and once this delicate balance is destroyed the stage of frank congestive failure may ensue.

Whether this particular state—elevated right ventricular end diastolic pressure in exercise associated with a normal increase in cardiac output—should be called the earliest stage of "heart failure" or the final stage of "physiologic" effort is perhaps a fine distinction. We believe, however, that it is worth while to emphasize the existence of this state, or stage in the progressive loss of cardiac reserve and suggest that it represents an aspect of right ventricular strain.

When symptoms were present at rest, hemodynamic alterations tended to be more marked than in the previous group. Furthermore evidence of pulmonary and peripheral congestion was frequently encountered. Left ventricular failure was demonstrated to be one of the important factors contributing to elevation of pulmonary artery pressures in some of these subjects. Although the whole subject of the effect of pulmonary congestion on lung function is being studied separately, one point can be made here about its influence on respiratory gas exchange. One might expect arterial oxygen unsaturation to occur particularly in the presence of rales. However, it is interesting that of 13 patients with rales only one half had arterial blood oxygen saturations below 95 per cent.

In this group of patients it was apparent that the finding of pulmonary hypertension was not diagnostic of any specific anatomic or physiologic condition and did not immediately clarify the nature of the pulmonary congestion. On the other hand, the clinical picture of right heart failure with its peripheral congestive phenomena had as its invariable physiologic cachet an elevation of right ventricular end diastolic pressure, despite considerable variation in the level of the accompanying pulmonary hypertension, cardiac output and plasma volume.

It is a well accepted fact that an increased blood volume is a common finding in right heart failure. The data presented here should not be considered at variance with this, since

many of these patients had received mercurial diuretics before study, perhaps reducing plasma volume. The importance of hypervolemia is evident in some of the patients in whom, with the recession of right heart failure, blood volume decreased. The fall in blood volume may have played a part in the decrease in pulmonary hypertension since it is logical to expect some decrease in pulmonary as well as peripheral venous blood volume. It may be that hypervolemia, especially of the pulmonary vascular bed, is a real factor in the maintainance of pulmonary hypertension in the presence of mitral stenosis.

Once patients reach the far advanced phase of irreversible congestive failure with very large hearts a consistently similar hemodynamic picture emerges, regardless of the variations in valvular lesions present. This is characterized by clinical and physiologic evidence of tricuspid insufficiency, very high pressures in the lesser circulation, and as a rule a very low cardiac output. This phase apparently represents total heart failure, myocardial contraction is markedly impaired and with cardiac pressures extremely high, and cardiac chambers very large, a profound state of vascular congestion and overstretched fibers with a large cardiac residual volume must exist. This surely is the end stage of decompensated rheumatic heart disease.

In considering in this paper the hemodynamic features encountered in rheumatic heart disease, we have grouped patients at various points along the clinical course of the illness in such a manner as to suggest the natural history of the disease. This grouping however, obscures the fact that little as yet is known or understood as to the sequence of hemodynamic events that any one individual patient may pursue. It is only by studying individual patients over many years that the actual course of hemodynamic changes may be charted, and one will learn for instance, whether or not pulmonary hypertension is progressive, recessive or stationary, and at what point the cardiac output becomes fixed.

Summary

1. Studies of cardiac function were made using the cardiac catheterization technic in 42 patients with rheumatic heart disease, of whom 16 had mitral stenosis, 12 had mitral stenosis and insufficiency, one had aortic insufficiency alone, and 13 had multiple valvular lesions.

2. Measurements were made of blood flow and blood pressures at rest, during exercise, and following the administration of Digoxin.

3. A steady state, which is mandatory when using the Fick principle, was demonstrated to be present only after five minutes of leg exercise in these patients.

4. Symptomatology gave a better indication of hemodynamic alterations than did the anatomic valvular lesions in this group of rheumatic subjects. Some of the asymptomatic individuals had normal hemodynamics, while the symptomatic patients consistently showed pulmonary hypertension, although the degree of this pressure elevation as well as the cardiac output was variable. When advanced congestive heart failure was present, the hemodynamic picture was uniform regardless of valvular lesions, and consisted of a low cardiac output, pulmonary hypertension, elevation of the right ventricular end diastolic pressure and hypervolemia.

5. The nature of pulmonary hypertension was explored in some of these patients and found to be due not only to mechanical mitral block, but also to left ventricular myocardial failure.

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The Mechanism and Incidence of Cardiovascular Changes in Paget's Disease (Osteitis Deformans)

A Critical Review of the Literature with Case Studies

By C. Franklin Sornberger, M.D., and Magnus I. Smedal, M.D.

Although abundant evidence of concomitant cardiovascular disease is scattered throughout the literature on osteitis deformans, appreciation of the etiologic relationship between the two diseases has been lacking. This paper shows that cardiovascular disease accompanying extensive osteitis deformans may result from: (1) excessive demand on the heart from increased vascularity of affected bones; (2) the influence of concomitant arteriosclerosis apparently exceeding the normal for the age concerned; (3) characteristic thoracic spine deformities which compromise cardiorespiratory function, and (4) hypertension. Fifty-four cases are presented. The incidence of cardiovascular disease exceeds that in the general population of the same age and corresponds with the extent of skeletal involvement.

MANY PHYSICIANS conversant with the osseous characteristics of Paget's disease are not well acquainted with concomitant changes in the heart and blood vessels which occur in the same disease. Incontrovertible evidence of such changes is scattered throughout the voluminous literature on osteitis deformans that has accumulated since Sir James Paget's original paper, but to date little attempt has been made to correlate these various findings and opinions, nor has any extensive study on the incidence of such changes been made. We have, therefore, reviewed the literature on Paget's disease with particular reference to the nature and incidence of the attendant cardiovascular changes, and presented a series of consecutive cases in which studies of heart size and electrocardiographic examinations have been made in an attempt to correlate previous observations and establish the incidence of related cardiovascular disease in osteitis deformans.

Occult,[1–3] monophasic,[4–10] monostotic,[11–15] and polyostotic or advanced classic forms of the disease have been described.[16–26] However, it is the vascular and cardiac changes that occur in the very extensive or classic form of the disease with which we are primarily concerned.

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Relationship between Paget's Disease and the Circulatory System

The characteristics of osteitis deformans, per se, have been thoroughly reported and discussed in periodicals and texts,[27–31] so that an attempt will not be made to elaborate on this aspect of the problem. The appreciation of the influence of osteitis deformans and attendant conditions on the cardiovascular system has been delayed and complicated by several factors: (1) there is a high incidence of degenerative vascular changes in the "normal" elderly population, which must serve as a basis for comparison; (2) the marked limitation of activity that usually accompanies the classic form of Paget's disease tends to mask the presence of cardiovascular changes in the group in which they would otherwise be most likely to manifest themselves; (3) the classic form of the disease is so uncommon (in contrast to the localized disease)[32, 33] that it is difficult to obtain a large series of cases for study; (4) deformities of the thoracic spine characteristic of the classic form of Paget's disease make the determination of the presence of cardiac

enlargement difficult on roentgenologic and physical examination.

The following conditions, any one or all of which may be present in a given case of osteitis deformans, either increase the work of the heart or decrease the ability of that organ to perform its function and, therefore, over a period of time, diminish cardiac reserve and predispose to enlargement and failure: (1) increased blood flow in the bony lesions of osteitis deformans in certain phases of the disease; (2) arteriosclerosis; (3) deformities of the thoracic spine and chest, and (4) hypertension.

Increased Vascularity and Hemodynamics in Osteitis Deformans

A. Incidence

Sir James Paget remarked the increased vascularity of affected bones, and described the appearance of the long bones in his first case which came to necropsy as follows: "The outer surface of the walls of the bones was irregular and finely nodular, as with external deposits or outgrowths of bone, deeply grooved with channels for the larger periosteal vessels, finely but visibly perforated in every part for the transmission of the enlarged small vessels. Everything seemed to indicate a greatly increased quantity of blood in the vessels of the bone."[22]

Increased heat over affected tibiae was recorded in three of the seven additional cases reported by Paget in 1882.[23]

Evidence of increased vascularity of affected bone in the form of increased redness, warmth, or dilated overlying vessels was noted by many subsequent observers,[8, 12, 15, 16, 34–44] and came to be recognized as a clinical feature of the disease.[40, 45–47] The replacement of bone by fibrous and vascular tissue[29, 48, 49] was observed to be accompanied by hyperemia, increased vascularity and also by fibrosis of the bone marrow.[1, 2, 6, 16, 17, 24, 32, 35, 44, 45, 50–55]

Instances of excessive heat and redness have been observed in this series, and have been interpreted as clinical evidence of increased blood flow in affected bone.

It is usually difficult to accomplish satisfactory hemostasis when it is necessary to operate on pagetic bone. Two patients in this series had surgical treatment and in both instances there was excessive bleeding. This problem has been encountered by others [39, 40, 55, 56] and emphasizes the degree of abnormal vascularity of bone affected by osteitis deformans.

Although the presence of excessive vascularity in bones affected by osteitis deformans was soon well established,[36, 39, 43, 54, 57, 58] the degree of increased blood flow, its relationship to the radiologic stage of the disease and influence on the general circulation remained to be determined.

In 1923, Sherwood Moore[39] made the first attempt to determine, quantitatively, the circulatory changes in Paget's disease by measuring the volume flow to the limbs. An average of many observations showed the blood flow to the affected limb to be over twice that to the sound limb, and he concluded: "Increased vascularity of bone in Paget's disease can be considered as established beyond doubt. . . . It certainly exceeds increased vascularity observed in infectious states of bone."

In view of the fact that recent experiments have emphasized the difficulties encountered in measuring the blood flow through extremities in human beings,[59] the work of Moore should, perhaps, be accorded more qualitative than quantitative significance, but it remains an important early observation.

Awareness of the effects of increased vascularity due to Paget's disease developed slowly. One of our patients, a 68 year old man, had extensive Paget's disease of 20 years' duration and when last admitted to the hospital was in congestive heart failure. The possibility of a relationship between the excessive blood flow due to Paget's disease and the congestive heart failure was considered, as shown by the entry of Dr. L. M. Hurxthal on the hospital record of December 27, 1943: "The right leg is hot, probably indicating marked blood flow there due to Paget's disease. This added blood flow may be a factor in heart failure."

The most comprehensive study of the vascular changes in bone affected by osteitis deformans and their influence on the general circulation has been made by Edholm, Howarth, and McMichael.[58] In 1945, they meas-

ured the cardiac output and bone blood flow in a 66 year old man who had advanced, extensive osteitis deformans accompanied by congestive heart failure of undetermined etiology. Left ventricular enlargement, marked capillary pulsation in the nail beds and a high pulse pressure were present. An electrocardiogram was normal. On venous catheterization, the right auricular pressure was elevated, and the cardiac output was 13.3 liters per minute. Occlusion of the circulation to the lower extremities (both of which were affected by extensive osteitis deformans) caused a drop in the right auricular pressure, pulse rate and cardiac output. Blood flow through the nutrient arteries of the affected bones was found to be from 10 to 20 times the normal. They concluded: "The data presented here indicated that there occurs in generalized* Paget's disease an increase in bone blood flow of sufficient magnitude to produce effects on the general circulation similar to those resulting from free arteriovenous communications. Further work is required to study the relationship between the increased flow and the radiologic stage of the disease. The absence of significant increases in cardiac output in cases of localized Paget's disease suggests that it is only when the disease becomes generalized that the circulation as a whole is greatly increased, and in such cases the signs of heart failure may develop."[58]

Further studies by Edholm and Howarth[57] provide additional evidence of excessive vascularity and bone blood flow in osteitis deformans. Two complete necropsies on cases that had been followed and studied revealed "tremendous development of the bone vascular system in the affected limbs which we further demonstrated by intra-arterial injections of radiopaque material." These observations were further substantiated by biopsy specimens and studies on the effect of intravenous epinephrine on skin temperature in the normal limb and in limbs affected by osteitis deformans. They concluded: "We have confirmed our previous findings that the total limb blood flow is very greatly increased when the bones in the limb are affected by osteitis deformans."

B. Effects

The increased vascularity that is characteristic of the involved portions of the skeleton in osteitis deformans[36] (at least in certain phases of the disease)[58] has been shown to have no significant effect on the general circulation when the area of bony involvement is small. When a large proportion of the skeleton is involved, the attendant increase in blood flow may be accompanied by elevation of the cardiac output[37, 58, 60] to several times the normal basal rate of approximately 4 liters per minute.[61, 62]

The factor of increased demand on the heart thus becomes an important consideration in extensive Paget's disease of long duration, in which case it reduces cardiac reserve, predisposing to enlargement and failure.[40, 63]

Arteriosclerosis and Cardiovascular Disease in Osteitis Deformans and the General Population

A. Incidence

The voluminous literature on the nature and incidence of arteriosclerosis attests to the controversial nature of the subject.[64–80] Statistics on the incidence of arteriosclerosis tend to be unreliable, particularly in the living, since there is not an entirely satisfactory method for the determination of its presence (once a definition of the nature of the process has been accepted) and various observers report their findings on the basis of different methods and standards.[67] In addition, intimal lesions are of more clinical importance than medial calcification,[68–70] and the problem is complicated by the fact that there are multiple causes of arteriosclerosis when the term is used in its liberal sense.[64, 68, 71–80]

Our interest in a possible relationship between arteriosclerosis and osteitis deformans was aroused from the observation that marked calcification of the arteries is nearly always found on the roentgenograms of patients with extensive Paget's disease, and from the fact that since the time of Paget, clinicians have

* Since osteitis deformans is not a systemic disease, "extensive" appears to be a preferable term.[8]

thought both the incidence and severity of arteriosclerosis to be greater in patients with osteitis deformans than among the general population of a similar age.[9, 27, 29, 39, 81]

The question of a real increase in the severity and incidence of arteriosclerosis in Paget's disease has not been adequately determined because so many observers were inclined to state their impression that the incidence and severity were out of proportion to the age groups concerned,[9, 12, 14, 24, 31, 35, 39, 45, 47, 50, 51, 55, 81–88] yet did not provide adequate statistical evidence. Still others dismissed the question with the caveat that the advanced age of the patient was in itself sufficient explanation for the severe arterioslcerosis,[21, 27] while some presented fairly sizable groups of cases supporting the contention that the incidence of arteriosclerosis is significant, the age of the patient notwithstanding.[16, 20, 28, 83, 89, 90]

For this reason, we have calculated the incidence of arterial calcification as seen in the roentgenograms of patients in our series with regard to the extent of bony involvement. The findings are, in turn, compared with the reported clinical and autopsy incidence of arteriosclerosis in the general population of the same age (fig. 1). Although our series is far too small to be of statistical significance, the fact that in local Paget's disease the incidence of arterial calcification on the roentgenograms is slightly less than the clinical incidence of arteriosclerosis in the general population of the same age,[91] yet in extensive Paget's disease, it exceeds the autopsy and clinical incidences for the age concerned,[91, 92] lends support to those who believe that the severity and incidence of arteriosclerosis in extensive Paget's disease exceed the normal, age notwithstanding.

B. Effects of Arteriosclerosis in Osteitis Deformans

1. Heart. Locke stated that in osteitis deformans, cardiovascular disease is undoubtedly the most common cause of death.[27] As the etiologic role of arteriosclerosis in chronic cardiovascular disease is well recognized, it will be alluded to only in broad outline.

Arteriosclerotic disease of the coronary arteries may lead to varying degrees of chronic myocardial ischemia.[82, 93–95] Decreased cardiac reserve, angina pectoris, myocardial fibrosis, dilatation with or without hypertrophy and, finally, failure may result, depending upon the degree of insult.[96–101] Coronary disease also predisposes to thrombosis, acute ischemia, conduction defects and infarction.[55, 94, 102] These may also result in dilatation, failure or death.[103]

Although the finding of increased incidence of calcification in the aorta and peripheral vessels is not direct evidence of excessive calcification of the coronary arteries, the arterial calcification in Paget's disease is not influenced by the proximity to involved bones.[90] Since in the "heterochronic aging"[16, 64, 78, 104] of the arterial tree the coronaries are known to be ahead of the peripheral vessels,[77, 104] excessive coronary artery calcification may be expected in Paget's disease.[105] Figure 2 shows the incidence of coronary artery disease in the general population in comparison with cardiac enlargement in osteitis deformans. Since not all cases of coronary disease have cardiac enlargement, it suggests that coronary disease in osteitis deformans must either exceed the normal for the general population of the same age or that other factors such as increased blood flow and chest deformities also play a part. We believe the excessive cardiac enlargement in Paget's disease to be the result of the combination of factors in most cases.

Arteriosclerosis and calcareous deposits which chiefly involve the aortic and mitral valves very often appear in advanced Paget's disease[27, 88, 90, 106, 107] and the resulting stiffness and deformity may impair the function of these structures.[94, 96, 101, 108–111] The work of the heart is thereby increased, most likely at the very time that the myocardium is deprived of an adequate blood supply by coronary artery disease.

A recent study by Harrison and Lennox[112] in England revealed that calcification of the mitral valve is more frequent in osteitis deformans than among the general population of a similar age group. These workers stated that intracardiac calcifications contribute to the high incidence of cardiovascular morbidity and mortality in Paget's disease.

In this connection, it is of interest that

Paget's disease was present in 3 of 12 cases of intracardiac calcification reported by Windholz and Grayson.[113] This is a much higher incidence than could be expected in view of the relative infrequency of Paget's disease. It should be noted that they[113] considered the calcifications to be unrelated to either rheumatic fever or arteriosclerosis.

2. Other Organs. The effects of arteriosclerosis in osteitis deformans are not limited to the heart. Symptoms which are referable to any organ or portion of the body may result from changes in its blood supply.

Peripheral arteriosclerosis causes a loss of elasticity in the vascular tree which results in benign or senile hypertension, characterized by a high systolic and more or less normal diastolic pressure, absence of progression or evidence of overt cardiac or renal damage and minimal retinal changes.[114] This type of hypertension is usually thought to have little effect on the heart itself,[68, 115] yet Burgess[114] has shown that the most frequent cause of death in these patients is cardiac failure, that they are subject to cardiac hypertrophy and enjoy somewhat less than normal life expectancy. Other authors have also stated that systolic as well as diastolic hypertension adds a burden to the heart.[60, 66]

Arteriosclerosis of the renal vessels and consequent interference with the renal blood supply has been shown to be a cause of hypertension.[66, 78, 116–120] Some authors consider hypertension to be associated with Paget's disease.[121, 122]

In the light of present knowledge it appears that a final decision cannot as yet be reached with regard to the relationship between arteriosclerosis that characteristically accompanies extensive Paget's disease and the development of hypertension of a degree that predisposes to cardiac hypertrophy and dilatation.

The presence of a diabetic type of glucose tolerance curve in Paget's disease has frequently been reported.[44, 46, 83, 89, 123, 124] The significance of this observation has recently been challenged but the mean age of the control group in this experiment exceeded that of the group with Paget's disease by 14 years.[125] Although a calculated correction was made for age discrepancy, the series was small and it appears likely that some degree of alteration in carbohydrate metabolism does occur in Paget's disease. The reason for such an alteration has not been demonstrated, but it has been suggested that arteriosclerotic changes in the kidneys, accompanied by a high renal threshold for glucose[83] or variation in the activity of the pituitary gland may play a part.[89]

Although some competent observers believe that arteriosclerosis is never a cause of diabetes,[126] other authorities state unequivocally that arteriosclerosis of the pancreas may be a cause of the milder type of diabetes which occurs in the aged.[78, 92, 127–129] In support of this premise, it may be recalled that the tendency for diabetes to appear parallels the progress of arteriosclerosis in Werner's syndrome.[130] It, therefore, is possible that the tendency for a diabetic type of glucose tolerance curve to develop in Paget's disease may be explained, at least in part, on the basis of arteriosclerosis of the pancreas. This interpretation should be tempered by the fact that glucose tolerance normally diminishes with advanced age[125, 131] and with marked limitation of activity,[131] both of which are often present in advanced osteitis deformans.

Deformities of the Dorsal Spine and Chest

A. Incidence

Severe cervicodorsal kyphosis accompanied by marked deformity and restriction of movement of the thoracic cage is recognized as characteristic of the advanced, classic form of osteitis deformans.[29, 31, 52, 54, 132] It was a prominent feature in 7 of the 12 cases reported by Paget up to 1882,[22, 23] and in 66 of 99 "authentic cases" in the literature up to 1900 reviewed by Packard, Steele and Kirkbride.[54] This association has subsequently been confirmed by numerous authors,[1, 4, 18–21, 24, 27, 52, 55, 81, 85, 88, 124, 133–135] and was present to some degree in two of the four cases of classic osteitis deformans in the present series.

B. Effects

Awareness of the direct and indirect effects of severe deformities of the cervicodorsal spine and chest on the cardiorespiratory system has developed very slowly, and in so far as osteitis deformans is concerned, began with the comments of Paget on his first case. He stated that the spine was curved and rigid, while "the chest became contracted, narrow, flattened from before backwards, and the movements of the ribs were lessened."[22] Again, in case 4 of his original series,[22] Paget noted that, "about a year before death the general health began to suffer from the thorax having become implicated in the disease. Gradually the chest became more contracted, and at last quite fixed; the breathing became more difficult until at last the respiratory apparatus altogether ceased." After observing further examples of respiratory embarrassment in his additional cases reported in 1882, Paget concluded that death "did not appear due in any degree to the disease of the bones unless it were that the difficulty in breathing was aggravated by the deformity of the chest."[23]

There are numerous references in the literature to disease of the chest caused by deformity and restricted movement of the thorax in Paget's disease.[1, 18, 24, 27, 40, 134] Occasionally, there has been further hindrance to respiration from paralysis of intercostal muscles as the result of a bony overgrowth at the neuroforamina.[47, 56]

Although severe deformities of the dorsal spine and chest became a recognized cause of right heart failure[136] and a materially shortened life expectancy[29, 111, 137–146] as well as decreased function of the lungs,[147, 148] the various mechanisms involved were not clarified until rather recently. Earlier observers had inclined to the view that the cause of right heart failure in these patients was mechanical, namely, loss of aid to the right heart from the normal respiratory movements, increased resistance in the pulmonary circuit due to kinking or compression of vessels and compression of one lung and compensatory emphysema of the other.[133–149]

The advent of pneumonectomy and the subsequent observation that obliteration of half of the pulmonary circuit failed to precipitate right heart failure made it clear that the anatomic interference with the pulmonary blood flow did not adequately explain the known facts concerning pulmonocardiac failure in the hunchbacked. Chapman, Dill and Graybiel made a step forward in the clarification of this problem by emphasizing the importance of decreased oxygenation.[139]

Further elucidation has recently been provided by the discovery of the fact that an abnormally low oxygen saturation of the blood has a marked vasoconstrictive effect on the pulmonary arterioles and precapillaries. Experimental evidence of this vasoconstrictive effect stems from the observation that in the normal individual, inhalation of half the normal oxygen concentration will double the pulmonary arterial pressure without raising the cardiac output.[150–152] McMichael pointed out that the oxygen saturation of the blood in patients with chronic emphysema is nearly always below 80 per cent, and may be as low as 30 per cent.[151] He discussed these findings in relation to right heart failure and emphasized, along with others,[100] that a rise in pulmonary arterial pressure causes more embarrassment to the right ventricle than a corresponding rise in systemic pressure does to the left ventricle. This is true because a rise in systemic pressure automatically enhances the coronary flow, whereas, the right ventricle is not benefited as a result of its increased work. McMichael summarized the effect of pulmonary vasoconstriction which results from relative anoxemia as follows: "Poor ventilation of the lungs may induce this vasoconstrictive reaction and this may be the key to the problem of many forms of pulmonary heart disease. The difficulty of moving a kyphoscoliotic thoracic cage with consequent limited ventilation may have the same action on the pulmonary arterial pressure as the poor ventilation of emphysematous lungs, or lungs in which the bronchioles and alveolar ducts are strangled by peribronchial lymphatic carcinoma."[151]

It may be stated, therefore, that in classic osteitis deformans, the frequent, severe deformities of the cervicodorsal spine and chest,

accompanied by fixation of the thoracic cage and respiratory distress, occasionally augmented by paralysis of intercostal muscles, may predispose to right heart failure through anatomic interference with pulmonary blood flow, and as a result of spasm of the pulmonary arterioles and precapillaries from the attendant low oxygen saturation.

Anemia in Osteitis Deformans

On the basis of pathologic reports, a significant degree of anemia might be expected as a complication in extensive Paget's disease because of replacement of bone marrow by fibrovascular tissue and encroachment on the marrow cavity by bony overgrowth and osteoid tissue. MacCallum[153] stated that, "The marrow actually loses its blood-forming elements and becomes converted into a vascular fibrous tissue which produces much soft, bone-like tissue." Numerous other authors have confirmed the fact that metaplasia and fibrosis of the marrow and encroachment on the marrow cavity are common in advanced osteitis deformans.[1, 9, 14, 18, 21, 24, 31, 44, 49–52, 54, 154]

These pathologic findings notwithstanding, marked anemia, attributable to osteitis deformans, is a rare occurrence. Because Paget's disease progresses very slowly, if at all, there may be time for compensatory phenomena to counteract the effect of the gradual loss of erythropoietic tissue from the bone marrow so that anemia, comparable to that found when marrow is replaced by neoplasm, is rarely seen. Whatever may be the reason, we have not found any cases of anemia due to Paget's disease in this series in which the red blood count and the hemoglobin reached less than 50 per cent of normal, which is considered necessary to cause cardiac enlargement from anemia.[155, 156] Moreover, we have been able to find only one case in the literature in which severe anemia was attributed to Paget's disease.[52] In this case, there was extensive replacement of the red marrow by fibrous tissue, and death resulted from "osteosclerotic anemia which developed as a result of Paget's disease." In view of its demonstrated infrequency, it appears that complicating anemia is not a significant cause of cardiac enlargement and heart failure in extensive osteitis deformans.

Report of Cases

This series is derived from the selection of all cases of osteitis deformans which appeared in the files of the New England Baptist Hospital from January 1, 1941, to December 31, 1947, and includes a detailed study of the records in each case. During this interval, there were 106 patients for whom a definite diagnosis of Paget's disease was made. Eighty-eight of these patients had been studied at the Lahey Clinic at some time before their hospitalization, and their outpatient records were also utilized for this study.

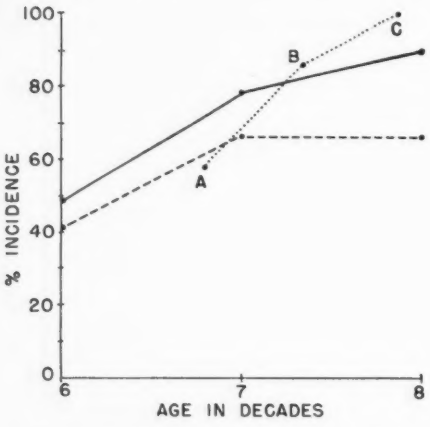
The incidence of cardiac enlargement and other studies are reported for 54 of the 106 patients for whom standard 72 inch posteroanterior chest films were available. The 52 patients for whom chest films were not taken, comprising a number in whom cardiac enlargement was found on physical examination, were not included in this series.

For the purpose of determining the influence of the extent of the disease on the cardiovascular system, the 54 cases were arbitrarily divided into three groups: (1) local disease, in which osteitis deformans was confined to one bone or anatomic part such as the skull or pelvis, (2) moderately extensive disease, in which the process involved more than one long bone or part, but less than the classic form, and (3) classic osteitis deformans, in which the skull, spine, pelvis and extremities were widely involved.

The mean age at examination was 58 years for group 1 (36 cases), 63.4 years for group 2 (14 cases) and 68.8 years for group 3 (four cases).

Because of the high incidence of degenerative vascular disease in the general population of the sixth, seventh and eighth decades, the age of the patients who have Paget's disease is an obstacle to the demonstration of a relationship between osteitis deformans and cardiovascular disease. Figure 3 shows the incidence of cardiac enlargement in the general population of various age groups as determined by physical examination. These findings were derived from

the examination of 100,924 unselected life insurance policy holders by one group[157] and 10,000 similar unselected life insurance policy holders by another group.[158] As the decades concerned. Comparison of these figures with the incidence of cardiac enlargement in Paget's disease as shown in figure 3 reveals the incidence in patients who had extensive osteitis deformans to be many times that of



····· ARTERIOSCLEROSIS IN PAGET'S DISEASE (SORNBERGER & SMEDAL)

—— AUTOPSY INCIDENCE ARTERIOSCLEROSIS IN GENERAL POPULATION (OPHÜLS, 1933)

--- CLINICAL INCIDENCE ARTERIOSCLEROSIS IN GENERAL POPULATION (WRIGHT, 1948)*

A LOCAL PAGET'S DISEASE

B MODERATELY EXTENSIVE PAGET'S DISEASE

C CLASSIC PAGET'S DISEASE

FIG. 1. The clinical incidence of arteriosclerosis in various stages of Paget's disease versus the incidence (clinical and autopsy) of arteriosclerosis in the general population. Age on this and subsequent graphs is by decade; thus, the seventh decade corresponds to age 60, and so forth.

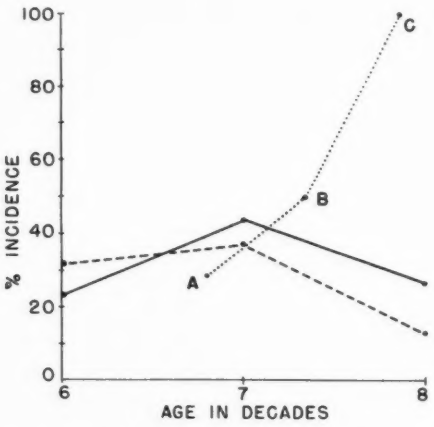
Dotted line: Arteriosclerosis in Paget's disease (Sornberger and Smedal).

Solid line: Autopsy incidence of arteriosclerosis in the general population (Ophüls, 1933).

Dash line: Clinical incidence of arteriosclerosis in the general population (Wright, 1948). (The author stated the incidence by decades *for each sex*. This graph represents the arithmetic mean of his figures for each decade.)

A: Local Paget's disease. *B:* Moderately extensive Paget's disease. *C:* Classic Paget's disease.

incidence in these groups was reported for each sex, and in the latter group for five-year periods, the incidence shown in figure 3 was derived by using the arithmetic mean for the two five-year groups and for each sex in the



····· CARDIAC ENLARGEMENT IN PAGET'S DISEASE (SORNBERGER & SMEDAL)

—— CORONARY HEART DISEASE (PAUL WHITE, 1947; BURCH and REASER, 1946)

--- CORONARY HEART DISEASE (CASSIDY, 1946)*

A LOCAL PAGET'S DISEASE

B MODERATELY EXTENSIVE PAGET'S DISEASE

C CLASSIC PAGET'S DISEASE

FIG. 2. The clinical incidence of coronary heart disease in the general population versus cardiac enlargement in various stages of Paget's disease (see text for explanation).

Dotted line: Cardiac enlargement in Paget's disease (Sornberger and Smedal).

Solid line: Coronary heart disease (White, 1947; Burch and Reaser, 1946).

Dash line: Coronary heart disease (Cassidy, 1946). (The author stated the incidence by decades *for each sex*. This graph represents the arithmetic mean of his figures for each decade.)

A: Local Paget's disease. *B:* Moderately extensive Paget's disease. *C:* Classic Paget's disease.

those in the general population *of the same age*.

Figure 4 shows the relationship between cardiac enlargement and the extent of bony involvement in osteitis deformans. There is a marked increase in the incidence of enlargement as the disease becomes more extensive, and as

seen from figure 3, this increase is much greater than could be expected solely from the age groups of the patients concerned. Of the cases with localized disease, 28 per cent had cardiac

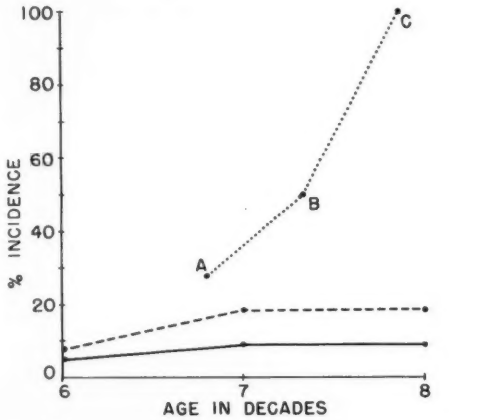


FIG. 3. The clinical incidence of cardiac enlargement in the general population versus cardiac enlargement in various stages of Paget's disease (see text for explanation).

Dotted line: Cardiac enlargement in Paget's disease (Sornberger and Smedal).

Solid line: Clinical incidence of cardiac enlargement in the general population (Sydenstricker and Britten, 1930). (The authors stated the incidence by decades *for each sex*. This graph represents the arithmetic mean of their figures for each decade.)

Dash line: Idem. (Proc. Life Ext. Examiners, 1939). (The incidence was stated by five-year periods. This graph represents the arithmetic mean for each decade.)

A: Local Paget's disease. *B:* Moderately extensive Paget's disease. *C:* Classic Paget's disease.

enlargement, whereas the groups with moderately extensive and classic osteitis deformans had 50 per cent and 100 per cent cardiac enlargement, respectively.

Since the use of life insurance examinees as representative of the general population may be questioned because they comprise a group from which the lowest economic classes are largely excluded, and since physical examination is less accurate than the teleroentgenogram for the determination of the size of the heart, further comparisons may be useful. Kretschmer and Butler[159] reported the incidence of cardiac enlargement from *all causes* to be 15.3 per cent in 314 patients who suffered from prostatic disease. Patients who have prostatic disease tend to fall in the same age group as those with Paget's disease, and when it is recalled that for a given age, males are usually

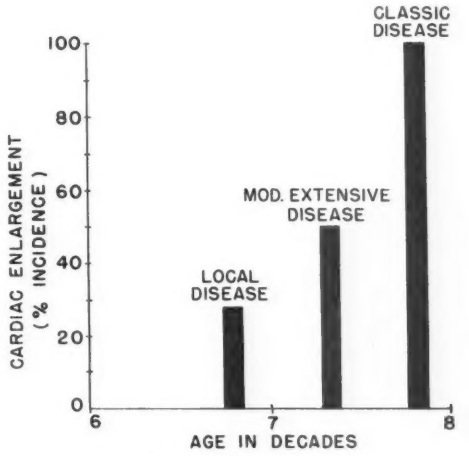


FIG. 4. The relationship between cardiac enlargement and the extent of bony involvement in Paget's disease.

more susceptible to coronary disease than females,[79, 99, 160] and that prostatic disease itself (when it causes obstruction) may be a cause of cardiac enlargement, the contrast with the incidence of cardiac enlargement in extensive osteitis deformans becomes even more significant.

There is further well documented evidence that overt heart disease and cardiac enlargement are not the rule in the aged general population. Willius[102] studied 700 patients whose ages varied from 75 to 96 years, and could not find clinical evidence of heart disease in 45 per cent; however, the incidence of congestive failure was 12.1 per cent. Boas[68]

discussed the aging of the cardiovascular system, and pointed out that in old age the body demands less oxygen, the caloric intake is less and the individuals in this group avoid extreme temperatures and physical activity. He concluded that such patients do not have a need for the great cardiac reserves of youth, and that usually, the functions of the heart and arteries suffice to meet the needs of the body under basal conditions in advanced old age.

A comparison of the incidence of cardiac enlargement in extensive osteitis deformans with that in the general population of the decades concerned, therefore, refutes the factor of age per se as an explanation for the increased incidence in Paget's disease. When age is discounted, it may readily be seen that the incidence of cardiac enlargement in osteitis deformans is correlated with the extent (and presumably the duration) of bony involvement (figs. 3 and 4). A summary of the reported incidence of cardiac enlargement and arteriosclerosis in Paget's disease may be found in table 1.

Electrocardiographic tracings were available in 21 of the 54 cases in this series. The incidence of normal tracings and those showing coronary disease in the various stages of bony involvement is consistent with the concept that cardiac disease is directly related to the proportion of the skeleton involved. A summary of the electrocardiographic findings may be found in table 2.

Figure 2 shows the clinical incidence of coronary heart disease in the general population in comparison with the incidence of cardiac enlargement in the various stages of Paget's disease. The incidence of cardiac enlargement in osteitis deformans exceeds the clinical in-

TABLE 1.—*Summary of Incidence of Arteriosclerosis and Cardiac Enlargement in Paget's Disease*

Author	Arteriosclerosis		Cardiac Enlargement		Evidence	Extent of Bone Disease	Age (mean, Yrs.)	Duration (mean, Yrs.)
	Number	Per cent	Number	Per cent				
Paget, 1877	1 of 1	100*	1 of 1	100*	Necropsy	+++	68	22
Hurwitz, 1913	—	—	2 of 6	33.3	Clinical	—	—	—
Smith, 1928	2 of 2	100	2 of 2	100	Necropsy	+++	70	—
Bortz, 1930	14 of 14	100†	9 of 14	64†	Necropsy	++ to +++	—	—
Kay, Levy-Simpson, Riddoch and Vilvandré, 1934	30 of 34	88	15 of 34	44	Clinical	++ to +++	55	9
Gutman and Kasabach, 1936	—	—	1 of 5	20	Clinical	+++ (1 case)	54	6
Clegg, 1937	1 of 1	100	1 of 1	100	Necropsy	+++	64	5
Schwarz and Reback, 1939	6 of 9	67	4 of 9	44	Clinical Necropsy	++ to +++	58	—
Turner, 1940	—	—	1 of 3	33	Clinical	+++	55	—
Wells and Holley, 1942	1 of 1	100§	1 of 1	100§	Necropsy	+++	59	6
Seligman and Nathanson, 1945	1 of 1	100	1 of 1	100	Necropsy	+++	64	13
Edholm, Howarth and McMichael, 1945	—	—	7 of 18	39	—	—	—	—
Burr, 1945	—	—	1 of 1	100§	Clinical	+++	59	—
Whalley, 1946	1 of 1	100	1 of 1	100	Clinical	++	66	5
Windholz and Grayson, 1947	—	—	2 of 3	67‡	Clinical	—	77.5	—
Rabiner and Hand, 1947	5 of 5	100	1 of 5	20	Clinical	+++ (1 case)	52	10?
Sornberger and Smedal, 1948	37 of 54	69	21 of 54	39	x-ray	+ to +++	59.6	—
	4 of 4	100	4 of 4	100	x-ray	+++	65	17.5
	12 of 14	86	7 of 14	50	x-ray	++	63.4	—
	21 of 36	58	10 of 36	28	x-ray	+	58	—

* Paget reported five cases, but only one in detail which came to autopsy.

† Bortz reported 21 cases, but only 14 came to autopsy.

‡ While there were three cases of Paget's disease in the series of 12 cases of intracardiac calcification, only two of the three were identified as examples of Paget's disease.

§ This patient had rheumatic heart disease with congestive failure.

cidence of coronary artery disease in the general population when the bony involvement is extensive, in which case it also exceeds the clinical *and autopsy* incidence of arteriosclerosis in normal subjects for the ages concerned (fig. 1). This difference becomes more significant when the fact that marked coronary artery disease may be present at autopsy without previous[93, 161] clinical evidence is considered, and when one considers that in 2,000 consecutive autopsies only 69 per cent of the patients who had significant coronary artery disease showed cardiac enlargement.[111] It is apparent, therefore, that coronary sclerosis, per se, in the degree which is normal for the age concerned, could not account for the entire incidence of cardiac enlargement in Paget's disease. The other factors which help to bring about this high incidence of enlargement in Paget's disease are thought to be the increased cardiac output that often accompanies extensive osteitis deformans,[37, 40, 58] and more severe arteriosclerosis than is warranted by age alone.[12, 29, 39, 82, 89, 90] Rarely, chest deformities and possibly hypertension related to arteriosclerosis may contribute to cardiovascular morbidity and mortality in advanced Paget's disease.

TABLE 2.—*Electrocardiographic Findings in Paget's Disease*

Stage of Disease (bony involvement)	Mean Age (at examination)	Number of Cases with Electrocardiogram	Normal		Coronary Artery Disease		Left Ventricular Hypertrophy	
			Number	Per cent	Number	Per cent	Number	Per cent
Localized	58.0	14	6	43	1	7	7	50
Moderately extensive	63.4	6	2	33	1	17	3	50
Classic	68.8	1	0	0	1	100	—*	—*
		—	–		–		—	
		21	8		3		10	

* The complication of bundle branch block prevented determination of presence of left ventricular hypertrophy.

METHODS AND SOURCES OF ERROR

It is realized that the figures presented on the incidence of cardiovascular disease in osteitis deformans do not represent a series large enough to be statistically significant. This will probably be true, however, of any one series owing to the relative infrequency of osteitis deformans in the moderately advanced and classic forms. In the meantime, these data may be accorded qualitative significance, and the determination of the precise incidence of cardiovascular disease in extensive osteitis deformans must await the publication of further studies.

The cardiothoracic ratio as measured on postero-anterior chest films, taken in an upright position at a distance of 72 inches, has been used as the index of cardiac enlargement in this series. It is generally conceded that this is an inexact method, although it is far more dependable than clinical findings.[162, 163] The chief source of error attendant upon the use of the cardiothoracic ratio lies in the fact that minimal enlargement may escape detection.[164] Since error from the use of this method would tend to result in finding *too few cases* of cardiac enlargement, employment of the cardiothoracic ratio appears justified.

The fact that chest films were made for all of the patients in this series may distort the incidence of cardiac enlargement. While many chest films are taken routinely, or for conditions unrelated to the heart, an indeterminate error will result from the fact that patients who have symptoms referable to the heart are often selected for chest films, and the apparent incidence of cardiac enlargement may thereby be increased. This error can be eliminated only by reporting a series in which chest films are taken routinely on all patients with extensive Paget's disease. However, this error is compensated to some degree by the use of the cardiothoracic ratio which does not indicate cases with minimal cardiac enlargement.

A possible source of error in the determina-

tion of the size of the heart in osteitis deformans is the deformity of the cervicodorsal spine and chest, commonly seen in the advanced or classic form of the disease. These deformities, when present, make the determination of the size of the heart, by roentgenologic or physical examination, difficult. To date, no way has been found to obviate this problem, except by autopsy, although it did not have any influence in this instance since only two cases in this series had marked cervicodorsal kyphosis, and in each, the cardiac enlargement was so great as to be beyond question.

Summary and Conclusions

1. An appreciation of the influence of osteitis deformans and concomitant conditions on the cardiovascular system has been retarded and complicated by several factors: (a) the high incidence of degenerative vascular changes in the normal elderly population, (b) the masking effect of limited physical activity on the symptoms of cardiovascular disease, and (c) the fact that the moderately advanced and classic forms of osteitis deformans are too uncommon to permit accumulation and study of a single statistically significant series of cases.

2. The incidence of cardiovascular disease is appreciably greater in extensive Paget's disease than among the general population, age notwithstanding, and is manifested by cardiac enlargement and marked arteriosclerosis.

3. Cardiac enlargement and arteriosclerosis are related to the extent of the bony involvement, and are more pronounced when the latter is extensive.

4. The mechanism of cardiac enlargement in extensive Paget's disease may be attributed to one, or more frequently, a combination of the following factors: (a) increased work of the heart as a consequence of the marked vascularity of bone in certain stages of osteitis deformans; (b) more frequent and severe arteriosclerosis than warranted by age alone, which may compromise the efficiency of the myocardium or valves, or both; (c) severe deformities of the cervicodorsal spine and chest which directly or indirectly embarrass the pulmonary circulation, and, on occasion, bring about right heart failure; (d) in some cases, hypertension which results from loss of elasticity in calcified vessels, or possibly from nephrosclerosis, may be an added burden.

5. There is not convincing evidence of a significant increase in the incidence of cardiac enlargement in localized Paget's disease.

6. Anemia as a complication of Paget's disease does not appear to produce cardiac enlargement in an appreciable number of cases.

7. It is suggested that arteriosclerosis of the pancreas may contribute to the production of a diabetic type of glucose tolerance curve in osteitis deformans and that Paget's disease should, in its extensive form, be added to the conditions (diabetes, myxedema, idiopathic hypercholesterolemia and hypertension)[68, 69, 77, 80, 116, 122, 160, 165, 166] which are considered to be accelerators of arteriosclerosis.

8. Patients in whom there is extensive osteitis deformans should be classified as having "potential heart disease"[167] and should have periodic physical examinations, chest films and electrocardiographic studies.

9. The determination of the exact incidence of cardiac enlargement and arteriosclerosis in extensive osteitis deformans must await further study of the subject and the compilation of a statistically significant number of cases.

Acknowledgments

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Measurement of Arterioles in Coarctation of the Aorta

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In cases of aortic coarctation determinations of the wall-to-lumen ratio were made for the arterioles of the thyroid, pancreas, kidney and periadrenal tissue and compared with those for arterioles from the same organs in control cases. As in primary hypertension, there was, on the average, an increase in the wall-to-lumen ratio in each of the regions studied in the cases of coarctation as compared with the same tissues of the control group. This means that for arterioles of the same wall size the lumen was narrower in the cases of coarctation than in the control cases.

IN RECENT YEARS the possibility of surgical treatment of coarctation of the aorta has stimulated greater interest not only in its early diagnosis but also in its clinical, pathologic, and physiologic characteristics. One of the most universally accepted facts has been the presence of hypertension in the upper extremities and "relative hypotension" in the lower extremities. The present study was undertaken with this premise in mind. The purpose has been to determine the status of the arterioles in coarctation of the aorta and to compare the findings above with those below the site of stenosis.

The background of this study is furnished by the many workers who have described the pathology of the arterioles in essential hypertension. Many of the early investigators[1-6] described various changes (hypertrophy, fibrosis, hyalinization, and so forth) of one or all three divisions of the arteriolar wall, and each investigator felt that a particular specific change was the primary pathologic process. In 1929 Kernohan, Anderson and Keith[7] reported their findings in 53 cases representing all grades of essential hypertension, in which they studied arteriolar changes in biopsy specimens taken from a pectoralis major muscle. They felt that fundamental structural changes were hypertrophy of the media, with an increased number of cells, proliferation of the endothelial cells occasionally with associated subendothelial proliferation, and hyperplasia with occasional splitting of the internal elastic lamina. In order to express accurately the degree of thickening of the arteriolar wall and the change in size of the lumen, they also made measurements of the walls and lumina of a large number of arterioles and expressed the change in terms of the wall-to-lumen ratio. ("Wall-to-lumen" will hereinafter be referred to as "W/L.") They found the W/L ratio in pectoral muscle of the normal subject to be 1:2. In benign hypertension it was 1:1.4, and in severe benign or early malignant hypertension, 1:1.1.

Subsequently, similar studies were carried out on the kidney,[8] myocardium,[9] pancreas, liver, gastrointestinal tract, spleen,[10] brain,[11] thyroid,[12] and skin[13] of patients with essential hypertension. These investigators obtained results comparable to those of Kernohan and associates and the results were summarized by Kernohan in 1939.[14] He felt that the thickening of the walls of the arterioles was not the cause but the result of hypertension. He concluded that the sequence of events in this pathologic process could be described as follows: (1) work hypertrophy of the musculature of the media occurs, with coincidental hypertrophy of the elastic lamina; (2) when the walls are sufficiently thick to impair nourishment, degeneration follows (the degree of impairment determines whether fibrosis, fatty degeneration, necrosis, or even liquefaction occurs); (3) increase in endothelial cells of the intima and increase in intimal connective tissue occur late and the latter may be actual or apparent, (4) the adventitia is frequently increased in thickness.

Abridgment of a thesis submitted by Dr. Painter to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Andrus[15] has objected to the use of the W/L ratio, saying this is an erroneous measurement. However, Moritz[16] in a detailed study has discounted his objections and feels that it is an accurate and worth-while determination.

Clinically the severity of hypertension in coarctation of the aorta is comparable to that occurring in patients with group I and group II essential hypertension. The degree of hypertension seen in patients with group III and group IV essential hypertension does not usually occur in patients with coarctation of the aorta.[17] Thus arteriolar changes would be expected to be minimal in coarctation as compared with those in the more severe cases of essential hypertension, but any definite and consistent change as compared with those in normal controls can be considered as significant.

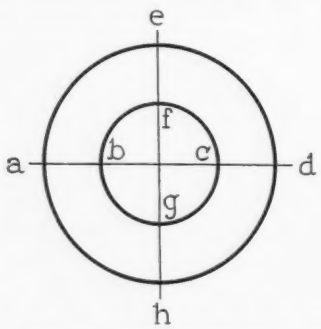

FIG. 1. Diagrammatic representation of a cross section of an arteriole. See text for explanation.

Graybiel, Allen and White[18] studied the arterial vessels in five cases of coarctation of the aorta in which the patients' ages varied from 20 to 33 years. They determined the W/L ratio of the vessels in the skin from the arm and leg as well as in biopsy specimens from the deltoid and gastrocnemius muscles. They concluded that there was no significant difference between the arterioles of the arm and of the leg in the cases of aortic coarctation which they studied. Although there was occasional slight intimal thickening and slight endothelial proliferation, they felt that the vessels were essentially normal in appearance.

On the other hand, Hines, Farber and Keith,[19] using the Kernohan criteria and technic, examined biopsy specimens of skin and subcutaneous tissue from the upper part of the arm and from the calf of nine ambulatory patients with coarctation of the aorta. In all cases of coarctation, as compared with the control cases, the thickness of the arteriolar wall was increased relative to the diameter of the lumen. Structural changes consisted of endothelial hyperplasia, proliferation and thickening of the inner elastic lamina, hyperplasia of the nuclear elements in the media, and apparent reduction in the size of the lumen. Not all arterioles were equally affected, although most of them showed some change from normal. Sections of skin from the calf revealed changes of the same degree as those from the arm.

MATERIAL AND METHODS

This study was carried out to determine the changes, if any, in the systemic arterioles in coarctation of the aorta as compared with a control group and to determine particularly what difference might exist between arterioles in the tissues above and those below the site of coarctation. The definition of an arteriole as outlined by Kernohan—namely, those arterial vessels with an outside diameter of 25 to 100 microns—was adhered to. A micrometer eyepiece was used over a high power objective, giving a magnification of 430 times (10 times 43). In figure 1 the external circle represents the external margin of the media of the arteriole while the inner circle represents the boundary of the lumen. The thickness of *ab*, *cd*, *ef*, and *gh*, respectively, were totaled and divided by four to give the average thickness of the medial and intimal components of the arteriolar wall. This figure was called the "thickness of the wall." The average value for the diameter of the lumen of the vessel was determined by adding *bc* and fg and dividing by two. The adventitia was not included in the measurements since this layer varied considerably in thickness. Ten arterioles in each tissue were measured in each case. Each section was examined routinely from left to right. The first 10 arterioles cut at right angles and suitable for measurement were used.

From the measurements obtained the ratio of the thickness of the wall to the diameter of the lumen was calculated for each arteriole and averages of these ratios for each tissue in each case were made. Then, in order that the thickness of the wall would always be represented by "1" in the ratios, the two elements of each ratio were divided by the first element (the thickness of the wall) to obtain the ratio in the form presented in this paper. Thus, for example, if the observed ratio of the thickness of the wall to the diameter of the lumen were 25:50, the two elements of this ratio would be divided by 25 to give the form 1:2 as used in this paper.

The tissues chosen for study were kidney, pancreas,

periadrenal tissue, and thyroid. Each tissue was sectioned and stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. All measurements were made on the latter sections since elements of the vessel are clearly defined.

TABLE 1.—*Average Wall-to-Lumen Ratios in 10 Control Cases*

Tissue*	Average of all controls	Range (average in individual cases)
Thyroid	1:1.98	1:1.61—1:2.27
Pancreas	1:2.68	1:2.16—1:3.54
Kidney	1:2.66	1:2.11—1:3.71
Periadrenal	1:2.34	1:1.88—1:3.20

* Ten arterioles were measured in each tissue studied in each case.

renal disease, and the blood pressure had been within normal limits. There were 10 control cases. Five of these were in the age group 10 to 19 years and the remaining five were in the age group 20 to 29 years.

TABLE 2.—*Average Wall-to-Lumen Ratios in Nine Cases of Aortic Coarctation*

Tissue*	Average of all cases	Range (average in individual cases)
Thyroid	1:1.78	1:1.46—1:2.24
Pancreas	1:2.35	1:1.71—1:3.44
Kidney	1:2.00	1:1.51—1:2.42
Periadrenal	1:2.10	1:1.81—1:2.40

* Ten arterioles were measured in each tissue studied in each case except that the thyroid gland was represented by only six cases.

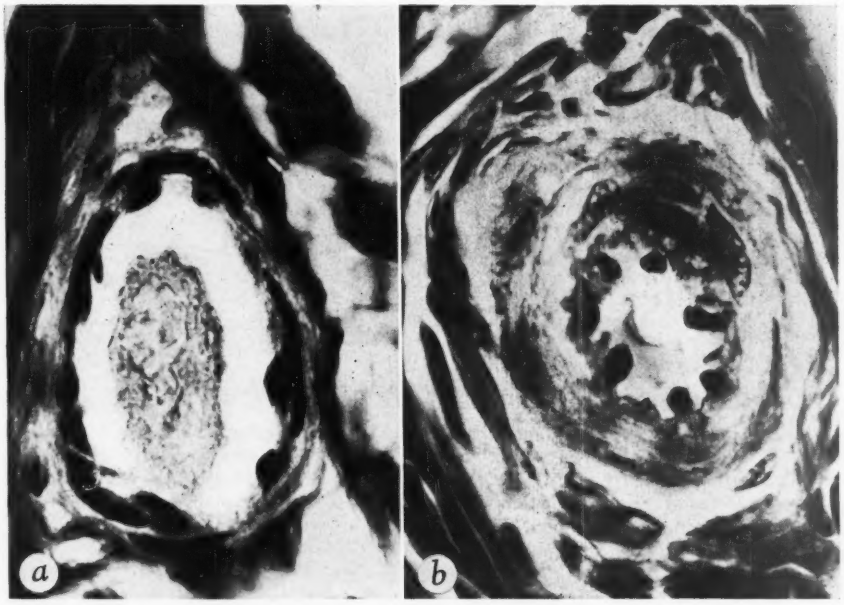

FIG. 2. Arterioles of the thyroid. The sections are stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. The average external diameter of each arterioles measures 50 microns (×1,175). (*a*) A normal thyroid arteriole with wide lumen and narrow media in a control case (subject aged 17 years). (*b*) An arteriole in the thyroid of patient aged 12 years of the coarctation group. There is medial hypertrophy with decrease in size of the lumen. Endothelial hyperplasia and a tortuous internal elastic lamina are evident.

Connective tissue appears bright red, muscle yellow, and elastic tissue a deep purplish blue.

Controls were chosen from necropsy cases in which death occurred accidentally or as a result of a rapidly progressive brain tumor. In none of these cases had there been coincidental cardiovascular or

Nine cases of coarctation were included in the study. The ages varied from 7 to 28 years. Of the cases in which the ages were less than 20 years, in one the age was 7 years and in the other four it ranged from 12 to 19 years. The remaining four cases fell into the age group 20 to 29 years. No cases

of coarctation of the aorta with co-existing bacterial endocarditis were included.

Results

In the cases of coarctation a wide variation in W/L ratio, as well as apparent changes, was observed from arteriole to arteriole in each tissue as well as from case to case. There did not appear to be any consistent differences in the two age groups.

A summary of the average figures for the W/L ratio for each tissue in the 10 control cases is given in table 1. Tissue from the pancreas and kidney and periadrenal tissue were available in all of the nine cases of coarctation. However, thyroid tissue was obtained in only six cases. The average figures for the W/L ratio for each tissue in the nine cases of coarctation are recorded in table 2.

On the average, medial muscular hypertrophy with decrease in the luminal diameter and intimal proliferation were more common in the coarctation group than among the controls (figs. 2 and 3); however, the average measurements in the coarctation group fell within the range of the control group, except in the case of the kidney. Accentuation and thickening of the internal elastic lamina were seen occasionally in the coarctation group.

Comment

Generally, in coarctation of the aorta the thickness of the wall of systemic arterioles increases relative to the diameter of the lumen. This change is most commonly associated with medial hypertrophy and narrowing of the lumen. Furthermore, these changes occur in the tissues below the coarctation as well as those above. The picture is similar in every way to those arteriolar changes occurring in essential hypertension of comparable degree as described by many authors.

These findings would seem to substantiate the theory that a generalized arteriolar hypertonus with resultant increase in peripheral resistance above and below the coarctation occurs in coarctation of the aorta. The high incidence of elevation of diastolic blood pressure in the

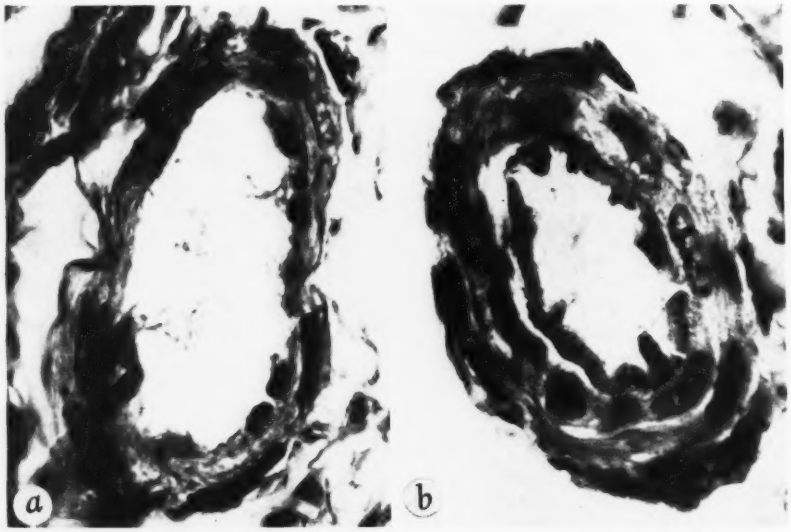

Fig. 3. Periadrenal arterioles. The sections are stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. The average external diameter of each arteriole measures 75.3 microns (×1,175). (*a*) An arteriole in the periadrenal tissue in a control case (subject aged 12 years). The media is thin with a wide lumen. (*b*) A periadrenal arteriole of a patient aged 7 years, of the coarctation group. There are medial hypertrophy, narrowing of the lumen, and thickening of the internal elastic lamina.

lower extremities, even though the systolic blood pressure may be low, has been pointed out by Steele[20] and others,[21] and in addition the resting blood flow in the upper and lower extremities has been found to be essentially normal in cases of coarctation of the aorta as compared with normal controls.[22]

While Graybiel and associates in their study found no difference in the vessels above and below the site of coarctation, no control group was reported in their paper. More recently the work done by Hines, Farber and Keith,[19] previously cited, would appear to be parallel and consistent with the results of the study presented here.

Conclusions

1. When the arterioles of the thyroid, pancreas, kidney and periadrenal tissue in cases of coarctation of the aorta were compared with the arterioles of corresponding tissues in control cases, generally it was found that the thickness of the arteriolar wall in cases of coarctation was increased relative to the diameter of the lumen.

2. Hypertrophy of the media, narrowing of the lumen, and apparent endothelial proliferation were the most common changes demonstrable.

3. Thickening of the internal elastic lamina was a less frequent change.

4. Not all arterioles were equally affected in each case.

5. There was no consistent difference between the age groups studied.

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Factors in the Production of Coronary Artery Disease

By J. C. Paterson, M.D.

The recent tendency to accept the syndromes of coronary artery disease as an indication of the presence or relative absence of coronary atherosclerosis in the living patient is open to serious objection. The production of these syndromes would appear to depend, not so much on the degree of coronary atherosclerosis, as on the presence of extraneous factors which precipitate occlusion. Of these factors, hemorrhage into atherosclerotic plaques is of major importance. The etiology of this lesion, and the manner in which it precipitates occlusion, are reviewed.

MUCH has been written during the past three years on the possible relationship between errors in lipid metabolism and the progression of atherosclerosis. Abnormalities in the cholesterol-phospholipid ratio and in the lipoprotein pattern of the blood have been incriminated, particularly, in the pathogenesis of the disease. The evidence obtained from cholesterol-fed rabbits has supported these claims, but it is extremely hard to obtain direct evidence in man. The stumbling block lies in the fact that an accurate assessment of the degree of human atherosclerosis can only be made on the autopsy table. This difficulty is well recognized; nevertheless, it has been the fashion in recent years to accept the syndromes of coronary artery disease as an indication of the presence or relative absence of coronary atherosclerosis in the living patient. When used in this way, these syndromes are open to serious objection.

It should be appreciated that coronary artery disease is not a pathologic entity; it is a clinical term for a number of symptom complexes which result from myocardial ischemia. Admittedly, at least 90 per cent of cases of myocardial ischemia are due to coronary sclerosis or its sequelae, but the qualification "or its sequelae" is important. Uncomplicated and progressive coronary atherosclerosis, resulting from the simple deposition of lipid materials over long periods, is not the common immediate cause of coronary artery disease. It is well known to pathologists that severe grades of coronary atherosclerosis are not incompatible with good health and normal heart action, while lesser grades of disease may be associated with occlusive phenomena. The classical studies of Blumgart and Schlesinger[1] have shown that the *gradual* reduction of the coronary lumen to a pinpoint size does not necessarily result in symptoms since it is compensated for by the opening up of a collateral circulation which is adequate for the ordinary activities of life. If these ordinary activities are exceeded, the anginal syndrome or acute coronary insufficiency may of course result; but this is not the usual way in which coronary artery disease is produced. On the contrary, it is usually precipitated by structural changes in atherosclerotic plaques, changes which have no apparent relation to lipid metabolism at the time of the catastrophe, but are more concerned with extraneous factors like coronary pressure, coronary blood flow and capillary fragility. Thus, the difference between an individual with clinically-evident coronary artery disease and a so-called normal individual lies, not so much in his grade of coronary atherosclerosis, as in the presence of these extraneous factors which precipitate occlusion. These factors, and the occlusive lesions which result, will be described in this paper. They are not particularly

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new, having been recognized now for over 15 years, but they are reviewed again, here, as they seem to have been ignored or forgotten by many workers in the field of arteriosclerosis.

Morphologic Aspects of Coronary Sclerosis

The structural alterations which lead to most of the complications of coronary atherosclerosis develop from changes in the blood supply to the arterial wall. The wall of a human artery, in health, obtains its nourishment from two sources. The adventitia and outer portion of the muscular coat are supplied with blood through the vasa vasorum which penetrate the arterial wall from without. The inner portion of the arterial wall, including the intima, is nourished in a different way, by the imbibition of nutrient materials from the blood circulating in the lumen of the artery. The intima of a normal human artery has therefore no true blood supply; but it develops one as the result of disease. Apparently by a compensatory mechanism, to supply the extra nutritional requirements of an abnormally thickened intima in the atherosclerotic process, capillaries grow into the intima and ramify within its substance.

These newly formed intimal capillaries are not derived from the usual vasa vasorum in the outer part of the arterial wall. They are abnormal structures and originate from the lumens of large arteries. Their direct origin from the arterial lumen was noted first in the aorta.[2] They have been shown by serial section technic to arise in a similar fashion in atherosclerotic coronary arteries,[3–6] and the full extent of their profuse ramifications in the inner parts of atheromatous plaques has been demonstrated by special injection methods.[7] The microscopic appearance of the origin and extent of intimal vascularization is illustrated in figures 1 and 2.

The peculiar position of these newly formed capillaries, in direct communication with the lumen of a major artery in which the pressure of blood is high, seems to be a major factor in determining their rupture. This point will be discussed later in this paper; but it is important to realize that intimal capillaries are exceedingly prone to rupture, and with their rupture disruptive hemorrhages within atherosclerotic plaques are produced.[4, 6] Serial section technic has proved that intimal hemorrhages are in fact intrinsic[5]; they are not due to the reflux of blood through a break in the lining of the artery, as was previously thought. Examples of intimal hemorrhages are shown in figures 3, 4, 5, and 6. Winternitz and his colleagues[7] have been so impressed with the frequency of hemorrhages in the intimal layer of arteries that they have suggested that they not only complicate the atherosclerotic process but may actually initiate it. Intimal hemorrhage cannot be accepted as a causative lesion in atherosclerosis (because the intima of normal human arteries is not vascularized), but as a complicating factor its importance is

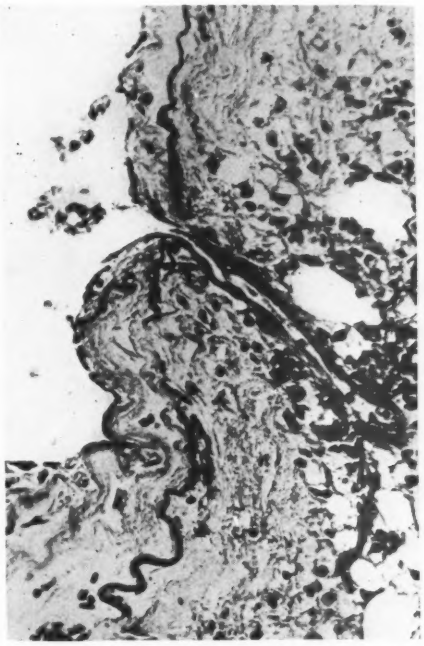

Fig. 1. High power photomicrograph of a sclerotic coronary artery showing a capillary arising from the arterial lumen, shown on the upper left, and penetrating the superficial layers of the thickened intima. The deeply staining round cells in the vicinity of the capillary are erythrocytes. (Hematoxylin and eosin stain. × 200.)

beyond question. Depending on the size of an intimal hemorrhage, its position within a plaque, and on coronary blood flow past the point of injury, the following sequelae may be produced:

1. Coronary artery spasm. This possible effect is highly speculative, and the only reason it is mentioned is because it has been suggested by others.[8] It has been postulated that, if a hemorrhage is sufficiently deep-seated and is close enough to the muscular coat, spasm of the artery may be initiated. An example of a deep-seated hemorrhage is shown in figure 4. If true, this mechanism may explain certain cases of sudden death which are otherwise obscure. But it must be an extremely rare phenomenon; in my series of many hundreds of intimal hemorrhages of the coronary arteries, there have been only two cases in which coronary occlusion might have been produced in this way.

FIG. 2. Low power photomicrograph of a coronary artery showing extensive vascularization of the inner portion of an atherosclerotic plaque. The arterial lumen is shown on the left. (Hematoxylin and eosin stain. × 20.)

2. Acceleration of the atherosclerotic process. Here, one is on safer ground. The addition of blood to an atherosclerotic plaque, like that illustrated in figure 5, must increase its bulk. Single hemorrhagic episodes, like this one, should produce little effect once the fluid portion of the blood is absorbed, but the gradual accumulation of the solid elements (such as cholesterol, blood pigment) from repeated hemorrhages into the same plaque should perceptibly increase its size. And in this regard it is to be noted that many atherosclerotic plaques contain blood elements in varying stages of dissolution, indicating the repetitive nature of intimal hemorrhages.

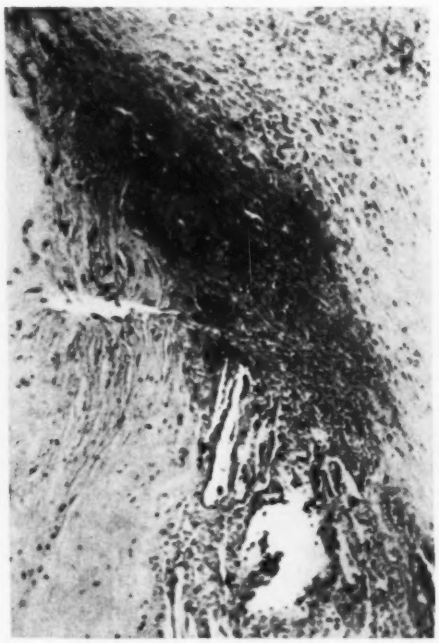

FIG. 3. Photomicrograph of a coronary artery showing an intimal hemorrhage into an atherosclerotic plaque. A portion of the arterial lumen can be seen at the upper left hand corner of the picture, and from it arises a capillary which enters the area of hemorrhage. (Hematoxylin and eosin stain. × 100.)

With a larger hemorrhage, like that shown in figure 6, there is a distinct possibility that the coronary lumen will be so reduced that the anginal syndrome might result. Symptoms which originate in this manner should be

transient, and one would expect them to disappear with the absorption of the hemorrhage.

3. Coronary occlusion from massive intimal hematoma. When hemorrhages are extremely large, the stenosis of the coronary lumen may be so marked that myocardial infarction, or acute coronary insufficiency with sudden death, occurs.[5, 9] This variety of coronary occlusion seems to be less common than has been reported in the literature.[10] In my series of occlusions which have been studied by serial section technic, the incidence of massive hematomata is less than 10 per cent. These large hemorrhages, however, have a clinical significance. It has been suggested that an ordinary hemorrhage which develops in a patient who is receiving anticoagulant therapy may progress to massive proportions because of abnormal blood coagulability.[11] This danger appears to have been exaggerated. Eight patients in my series who succumbed from coronary artery disease at a time when they were receiving dicumarol have been studied recently. An intimal hemorrhage was noted in each case, but in none was it of large size. Indeed, the hemorrhages were indistinguishable in their bulk from those seen routinely in autopsies on patients who had not received anticoagulants. It would appear that the production of a massive intimal hematoma depends on factors other than blood coagulability.

FIG. 4. Low power photomicrograph of an intimal hemorrhage into the deeper portion of an atherosclerotic plaque of a coronary artery. It lies close to the muscular coat. (Heidenhain stain. × 10.)

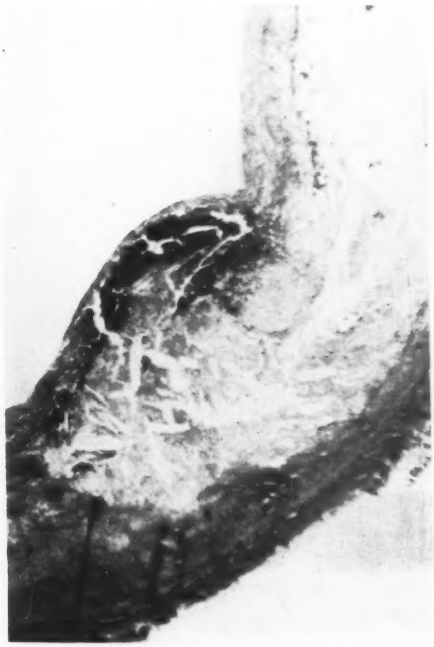

FIG. 5. Low power photomicrograph of a small hemorrhage into the superficial layers of a sclerotic coronary artery. The hemorrhage has caused a slight bulging of the plaque into the arterial lumen, which is shown on the upper left. (Heidenhain stain. × 10.)

4. The initiation of coronary thrombi. This complication of intimal hemorrhage is the most important of all. Providing that suitable conditions of stasis and eddying of blood exist at the point of hemorrhage (and these may be supplied by the shape and size of an atherosclerotic plaque which projects into the arterial lumen), thromboplastic substances which are liberated from the area of tissue disruption may then become operative. Thrombus precipitation may occur in several ways, as has been described in detail elsewhere,[4, 5,

[6, 12] but, regardless of the exact mechanism, everyone who has worked intensively on the subject agrees that the usual precipitating lesion of thrombosis, not only in coronary arteries, but in other arteries as well, is hemorrhage into an atherosclerotic plaque.[4, 5, 6, 10, 12, 13, 14] Skepticism still exists, of course, in certain quarters.

FIG. 6. Low power photomicrograph of an intimal hemorrhage of moderate size. The arterial lumen is shown on the left. The size of this atherosclerotic plaque must have been increased significantly by the hemorrhage. (Hematoxylin and eosin stain. × 15.)

It has been suggested, for example, that a hemorrhage which lies at the point of thrombosis may be the result, rather than the cause, of the thrombus; that it represents a form of hemorrhagic infarction of the vessel wall where it has been deprived of its blood supply by the occluding mass. This argument is refuted by the demonstration of hemorrhages at points where there is no associated thrombosis (as in figs. 4, 5, and 6).

Skepticism exists on still another score. Some pathologists will concede that an intimal hemorrhage may initiate thrombosis in certain cases, but they are not impressed with its frequency in this respect. Here again, some fairly exact data can be quoted. From a consideration of the figures given in table 1, it would appear that the incidence of intimal hemorrhage in any series of cases of coronary thrombosis will depend entirely upon the pains that are taken in searching for them. If thrombosed segments of arteries are sectioned serially at close intervals, the incidence of hemorrhage in relation to thrombus is as high as 90 per cent; but if only occasional random

TABLE 1.—*Incidence of Intimal Hemorrhage in Coronary Thrombosis Using Different Pathologic Technics*

Investigator	Pathologic Technic	Cases of Thrombosis Studied	Intimal Hemorrhages	
			Number	%
Paterson (1941)	Serial section at short intervals	58	52	89
Horn and Finkelstein (1940)	Many sections	123	64	52
Nelson (1941)	Many sections	10	9	90
Paterson (1950)	Many sections	34	21	62
Yater et al (1948)	Occasional sections	158 (?)	26 (?)	16

sections are studied through the thrombus (as in the series of Yater and co-workers[15]) the incidence falls to less than 20 per cent. The variation between these results can easily be explained. Intimal hemorrhages are often quite small, so small that they can only be demonstrated by serial sections at fairly close intervals. If they were usually large, and easily demonstrable by random sections, they would probably have been observed and described long before 1936.[4]

Perhaps the most impressive evidence of the relation of intimal hemorrhage to thrombus precipitation is obtained from a study of serial sections of coronary thrombi. When a throm-

bus has been traced to its point of initial deposition, it will sometimes be found to occupy only part of the lumen, and here it is attached to the endothelium immediately adjacent to a point of hemorrhage. Examples of this close relationship of thrombus to hemorrhage are shown in figures 7 and 8.

FIG. 7. Low power photomicrograph of a thrombosed coronary artery. The thrombus occupies only part of the arterial lumen, shown on the upper left, and it is attached and suspended at a point where a small hemorrhage has occurred into an atherosclerotic plaque. (Heidenhain stain. × 10.)

FACTORS INVOLVED IN THE RUPTURE OF INTIMAL CAPILLARIES

From the foregoing it appears certain that the rupture of intimal capillaries with the formation of intimal hemorrhages is the usual lesion in the production of the complications of coronary atherosclerosis. In the final analysis, then, the causes of capillary rupture in these locations are the usual causes of coronary artery disease. These causes are, admittedly, highly debatable. They will probably not be definitely established until they can be studied under controlled experimental conditions, and studies of this type must await the production of full-blown coronary atherosclerosis, with vascularized plaques, in susceptible animals. In the meantime, there are two schools of thought. First, there are those who regard capillary rupture as a purely fortuitous event in the course of atherosclerosis; who claim that it cannot be predicted, prevented or treated.[16] The other school

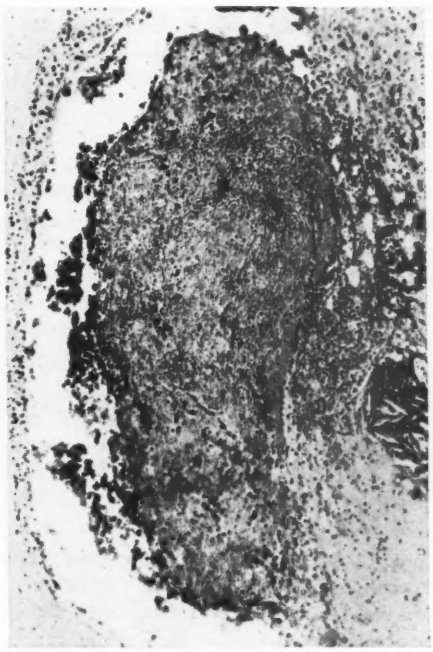

FIG. 8. Photomicrograph of a thrombosed coronary artery. Part of the arterial lumen, shown on the left, is still patent, and the thrombus is attached adjacent to an intimal hemorrhage. (Hematoxylin and eosin stain. × 50.)

has a more optimistic outlook. It holds that capillaries in these locations rupture from definite causes, and that these should be sought for industriously. Certain hypothetic factors have already been suggested,[6, 12] but the subject deserves more attention than it has received in the past.

It is apparent that an intimal capillary, like that shown in figure 1, may rupture from three general causes, operating individually or in combination: (1) from abnormally high pres-

sure within its lumen; (2) from abnormal fragility of its wall; and (3) from lack of support from the adjacent tissues. Arguments which support each of these hypothetic factors have been given in detail elsewhere,[6, 12] but only two of them will be summarized here.

Intracapillary pressure appears to play a major role in the rupture of intimal capillaries. These capillaries are peculiar in that they lie in direct communication with the lumen of a large artery in which the pressure of blood is normally high, and this high pressure will be transmitted, to a degree, into the capillaries themselves. If persistent hypertension is present, intracapillary pressure should be correspondingly increased, and there should be imminent danger of capillary dilatation and rupture. Intimal hemorrhages should therefore be more numerous in individuals with persistent hypertension that in those with normal blood pressures. This is, in fact, the case, as has been reported elsewhere[12]; and it may therefore be deduced that the transient elevations in blood pressure which accompany excessive exertion or emotion will have a similar effect in producing intimal hemorrhages.

The role of capillary fragility also deserves some comment. Many factors may increase the fragility of these small vessels. Some of these cannot be corrected, but those which are due to nutritional disturbances can. Possible deficiencies in vitamin C therefore deserve consideration, and recently it has been claimed that abnormal capillary fragility, in general, can be corrected by the administration of rutin. It has been stated that this material will protect the capillaries of the eye in hypertensive retinopathy, and the capillaries of the brain in hypertensive encephalopathy.[17] If true, rutin should be equally effective in protecting capillaries in atherosclerotic plaques. Obviously, carefully conducted and well controlled clinical trials are needed to assess the validity of these claims and assumptions.

Comment

The evidence reviewed in this paper suggests strongly that other factors besides atherosclerosis play a major part in the production of coronary artery disease. All of these extraneous factors have probably not yet been elucidated, but an important one has: the rupture of capillaries within atherosclerotic plaques seems to play a major role in determining whether or not an individual with coronary sclerosis will present signs and symptoms of myocardial ischemia. It follows that these signs and symptoms cannot be accepted as a measure of the severity of the atherosclerotic process, per se, in the coronary circulation. This conclusion has an important application to current investigations on the relation of errors in lipid metabolism to atherosclerosis. To use coronary artery disease as a criterion in these studies means that one is measuring not only atherosclerosis but these extraneous factors as well. Obviously, a more critical method of assessment is needed in this field of research. In my opinion, this can be done only by comparing serial blood lipid levels obtained during life with an accurate estimate of the severity of atherosclerosis as revealed at autopsy. In carrying out an assessment of this type, two points must be borne in mind. Since atherosclerosis is a disease which may take years to develop, and may persist for some time after the causative agent has ceased to act, the serial determinations of the blood lipids should be made over long periods. And it would be helpful if technics could be devised for estimating the severity of the disease at autopsy which are more accurate than the crude methods of grading in use today.

However, future research on atherosclerosis should not be confined to the chemistry of the blood lipids. It should include studies on arteries—on the tissues which are actually affected by the disease. In this regard, the causes of capillary rupture in atherosclerotic plaques demand attention. Statistical studies carried out recently by Morris[18] suggest that the incidence of coronary occlusion in England has increased during the past 40 years while the over-all severity of coronary atherosclerosis for the same period has declined. If one accepts the thesis that coronary occlusion is usually the result of extraneous factors which lead to the rupture of capillaries in the walls of arteries, and is not usually due to coronary

clerosis, per se, there is no inconsistency in this nteresting report from England. Indeed, until atherosclerosis is completely eradicated from he human race, or is so inhibited that it eaches no more than slight proportions, the omplications which have been described in his paper will remain with us: atherosclerotic plaques of any size will continue to become ascularized, intimal capillaries will continue o rupture, and the sequelae of intimal hemorhage will continue to occur. In the circumstances, it seems reasonable to suggest that the causes of capillary rupture in these locations deserve more attention than has been given hem in the past.

Summary and Conclusions

Evidence is reviewed to show that the signs and symptoms of coronary artery disease cannot be accepted as a measure of the degree of coronary atherosclerosis in the living patient. The production of these symptom complexes is a reflection, not necessarily of the degree of coronary sclerosis, but of certain extraneous factors which result in the rupture of intimal capillaries, the formation of disruptive hemorrhagic lesions within atherosclerotic plaques, and in the production of occlusive lesions. The urgency in elucidating the causes of capillary rupture in these locations is stressed.

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Oximetry in Congenital Heart Disease with Special Reference to the Effects of Voluntary Hyperventilation

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An oximeter has been used to measure the arterial oxygen saturation of patients with a variety of congenital heart anomalies. The effects of exercise and oxygen administration have been of value in ascertaining the presence of a venous-arterial shunt. The rise in arterial oxygen saturation during a vigorously performed voluntary hyperventilation appears to offer a means of gaging the extent to which the pulmonary circulation may be increased; a less than normal increase has only been found in the presence of pulmonic stenosis or in some instances of pulmonary hypertension and a relatively fixed pulmonary resistance. The results of hyperventilation are sufficiently distinctive to be of diagnostic value in cases of Fallot's tetralogy, Eisenmenger's complex, isolated pulmonic stenosis, pulmonic stenosis with intact ventricular septum and patent foramen ovale, and Ebstein's anomaly of the tricuspid valve with patent foramen ovale.

THE CHANGES in arterial oxygen saturation during exercise and oxygen administration have recently become an integral part of the study of congenital heart disease.[1–7] A low arterial saturation at rest or a fall during exercise has been associated with venous-arterial shunts. A failure to reach full arterial saturation and an unduly prolonged time to reach maximal saturation during oxygen administration have been accepted as evidence of large venous-arterial shunts. We wish to present the effects of voluntary hyper-ventilation on arterial oxygen saturation and to discuss the possibility of using this procedure as a diagnostic test.

METHODS AND MATERIAL

Arterial oxygen saturation was measured by an ear oximeter designed by Wood and Geraci[8] (Waters-Conley Absolute Reading Oximeter). Readings were made after a period of rest and a sufficient time to heat the ear. These were repeated at intervals until consecutive readings were constant. Oxygen (100 per cent) was administered through a mask for at least five minutes and continued for a longer time in many of the cases with cyanosis, the patient being in a recumbent position. Voluntary hyperventilation was carried out for one minute in the sitting position. The patient was shown how to breathe as rapidly and as deeply as possible and during the test was exhorted to make a maximum and constant effort. The exercise consisted of stepping up and down a platform 9 inches high 30 times in one minute. The changes in arterial oxygen saturation were called out by one observer and noted by another against time recorded by a stop-watch, and were followed after the completion of the test until the saturation had returned to its resting level. The oximeter was reset with each change of posture and during recovery from the test. A sufficient time was allowed between each procedure to enable the patient to recover. Movement of the oximeter ear-piece during the exercise test was prevented by fixing the cables to the head of the patient by means of a bandage.

Twenty-five normal subjects (10 males and 15 females) between the ages of 18 and 35 years were subjected to the above procedure and their results used to establish normal limits.

Cooperation and the ability to undertake a certain degree of effort were necessary for the performance of the exercise and voluntary hyperventilation. The results from the latter test were dependent upon the vigor with which it was performed and failure to do so was the most frequent cause for rejection from this series.

The congenital heart anomalies studied consisted of the following types with the number in each group in parenthesis: Atrial septal defect (5); high ventricular septal defect (2); Eisenmenger's complex (4); isolated pulmonic stenosis without septal defects (2); Fallot's tetralogy and variants (8); pulmonic stenosis with intact ventricular septum

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and patent foramen ovale (4); Ebstein's anomaly of the tricuspid valve with patent foramen ovale (2); patent ductus arteriosus with partial reversal of shunt (2). (See table 1.) It has been considered advisable to distinguish between an atrial septal defect and a patent foramen ovale in the conditions studied, although this cannot be decided by clinical and cardiac catheterization findings. An atrial septal defect allows a free communication between the left and right atrium whereas a patent foramen ovale has a valve-like action[9] which will be partial or complete depending upon the size of the foramen. Both pulmonic stenosis with intact ventricular septum[16, 17] and Ebstein's anomaly[11] are so commonly (if not invariably) associated with a patent foramen ovale when a defect between the atria exists that it has been described as a patent foramen ovale in preference to an atrial septal defect. The possible significance of the valve-like action of the patent foramen ovale in the results obtained will be discussed.

The diagnosis of atrial septal defect had been confirmed by venous catheterization of the heart. The cases of high ventricular septal defect and Eisenmenger's complex were considered together because of the similarity of the findings obtained by cardiac catheterization. Systolic and diastolic hypertension were present in the pulmonary artery, and pulmonic stenosis was excluded by the absence of a systolic pressure increase as the catheter was withdrawn from the pulmonary artery to the right ventricle. A ventricular septal defect was suggested by the finding of an oxygen content of blood from the right ventricle exceeding that from the right auricle by more than 1 volume per cent, by catheterization of the aorta from the right ventricle, or by early opacification of the aorta during angiocardiography. The criteria for classifying a case as one of Eisenmenger's complex as opposed to a high ventricular septal defect was a resting or effort induced arterial unsaturation in the former. Four of the six cases of high ventricular septal defect and Eisenmenger's complex had undergone cardiac catheterization. An angiocardiogram had demonstrated a high ventricular septal defect by early opacification of the aorta in one case in which this had not been shown by blood studies. The aorta had been catheterized from the right ventricle in two cases. Typical clinical, radiologic and electrocardiographic evidence of Eisenmenger's complex was present in the two remaining cases (M. J. and C. G.).

Isolated pulmonic stenosis had been demonstrated by cardiac catheterization in two cases. Blood oxygen studies excluded the presence of arteriovenous and veno-arterial shunts.

Six cases were considered to have Fallot's tetralogy. Pulmonic valvular or infundibular stenosis had been demonstrated by catheterization in four cases (S. C., C. W., N. F. and D. G.). An over-riding aorta had been catheterized in one of those cases (N. F.), while an angiocardiogram had revealed a similar defect in another (C. S.). The diagnosis of Fallot's tetralogy was confirmed at postmortem in case C. W., who died postoperatively. Two cases were diagnosed on clinical, electrocardiographic and radiologic findings of this condition (G. T. and N. N.). One of these cases of Fallot's tetralogy (G. T.) had a murmur of patent ductus arteriosus. Two cases were considered to have pulmonary atresia, an over-riding aorta and well developed (clinical and radiologic) findings of a bronchial artery collateral circulation to the lung (V. H. and J. S.). This variant of Fallot's tetralogy is generally referred to as "pseudo-truncus arteriosus." A high ventricular septal defect was shown by catheterizing the aorta in case J. S., and pulmonary arteries could not be found at operation.

The diagnosis in four cases was pulmonic stenosis with intact ventricular septum and patent foramen ovale. Case V. A. showed pulmonic stenosis on cardiac catheterization. A blood sample taken from the left auricle showed an oxygen saturation similar to that of the femoral artery blood, indicating that a venous to arterial shunt took place entirely through an atrial septal defect. The diagnosis of this condition was confirmed at autopsy in one case (T. R.) in which infundibular stenosis of the right ventricle and a widely patent foramen ovale were present. Clinical evidence of pulmonic valvular stenosis was present in two cases (P.B. and B. M.) and an atrial septal defect was demonstrated during cardiac catheterization.

Ebstein's anomaly of the tricuspid valve with patent foramen ovale was considered to be present in two cases.[11] The details of these cases have been published separately.[12] One case was cyanotic at rest while both showed a marked reduction in arterial saturation during effort. Cardiac catheterization showed normal pressures in the pulmonary artery, absence of pulmonic stenosis, and the division of the right ventricle into two distinct pressure zones. The pressures in the proximal (or inflow) part of the right ventricle and right auricle were similar. That the pressure was actually recorded from the proximal part of the right ventricle was indicated by the position of the catheter tip well to the left of the vertebral column during fluoroscopy. The catheter had been withdrawn from the pulmonary artery to this site and could not have entered any other chamber than the right ventricle. The catheter was withdrawn from this site well to the right of the vertebral column and under these circumstances was considered to be in the right auricle. These changes were demonstrated by a continuous pressure tracing from pulmonary artery to right auricle in case M. H. It was concluded that the right ventricle was divided by a displaced tricuspid valve. The only possible shunt capable of explaining the cyanosis on the basis of findings at catheterization was a venous-arterial shunt through a patent foramen ovale.

Two cases were diagnosed as patent ductus arteriosus with partial reversal of the shunt. The classical diastolic component of the murmur of patent ductus arteriosus was absent, yet cardiac catheterization demonstrated the presence of an aortic to pulmonary artery shunt. The pressures in the systemic and pulmonary artery circulations were such that a pulmonary artery to aortic shunt was possible. The reversal of the shunt was demonstrated in case D. H. by the finding of a higher saturation in the right

TABLE 1.—*The Effects of Voluntary Hyperventilation, Exercise and Oxygen Administration on the Arterial Oxygen Saturation (Per Cent)*

Diagnosis	Initials	Age yrs.	Sex	Arterial Oxygen Saturation (per cent)													
				Voluntary Hyperventilation				Exercise				Oxygen					
				0	20	40	60	0	20	40	60	0	1	2	3	4	5
				seconds				seconds				minutes					
Atrial septal defect	H. C.	13	F	91	92	92	93	91	91	91	92	91	93	94	94	94	94
	G. H.	27	F	94	95	96	96	92	94	94	94	94	97	97	97	97	97
	A. S. P.	56	F	93	94	96	96	92	92	92	88	93	101	100	100	100	100
	E. R.	18	F	93	94	95	95	90	92	92	88	93	98	98	98	98	98
	P. W.	13	M	93	96	98	98	93	94	92	94	93	100	100	100	100	100
High ventricular septal Defect & Eisenmenger's complex	F. A.	12	F	93	95	95	95	93	93	92	92	93	97	97	96	96	96
	C. J.	11	F	94	95	96	96	93	94	93	93	94	97	97	97	97	97
	C. F.	11	M	92	93	93	94	93	91	88	84	95	99	100	100	100	101
	M. J.	20	M	90	89	83	90*	93	92	86	86	92	97	98	99	99	99
	C. G.	28	F	83	80	80	79	83	79	73	66	82	88	88	88	88	88
	A. S.	21	F	79	80	76	75	80	71	58	40	83	87	91	89	89	89
Isolated pulmonic stenosis	B. M.	10	F	94	95	96	96	94	95	95	94	94	97	98	98	98	98
	I. R.	7	M	91	92	93	93	—	—	—	—	92	96	96	96	96	96
Fallot's tetralogy	S. C.	18	F	66	61	60	62	66	58	45	36	61	68	68	70	72	75
	S. C.	(Postop.)		89	90	89	88	91	91	90	86	91	97	98	98	98	98
	C. W.	33	F	66	64	63	60	50	46	40	36	68	70	70	72	73	74
	N. F.	7	F	69	70	68	68	69	70	66	64	70	74	76	77	77	77
	R. N.	7	M	90	91	87	87	90	89	87	84	90	97	97	97	97	97
	†G. T.	20	F	90	90	88	87	89	86	76	69	91	101	102	102	102	102
	D. G.	13	M	75	76	75	73	70	69	67	66	62	73	73	73	76	76
	‡V. H.	7	M	80	81	78	79	80	78	74	72	80	87	88	88	88	88
	‡J. S.	7	M	84	85	84	84	80	78	72	69	85	89	91	91	91	91
Pulmonic stenosis with intact ventricular septum & patent foramen ovale	P. B.	13	F	81	82	82	82	79	73	65	61	81	87	88	90	90	90
	T. R.	55	M	78	78	78	78	—	—	—	—	—	79	81	82	82	82
	V. A.	24	F	84	87	85	84	85	80	70	63	86	93	96	97	97	98
	B. M.	22	M	81	81	83	81	81	78	75	73	80	86	88	88	88	88
Ebstein's anomaly with patent foramen ovale	M. A.	21	F	87	91	92	93	87	85	80	77	91	96	97	97	97	97
	I. N.	20	F	67	70	72	76	72	66	68	59	72	84	86	86	86	86
Patent ductus arteriosus with partial reversal of the shunt	H. G.	16	F	93	96	96	96	93	91	90	89	93	98	99	98	98	98
	D. H.	34	F	87	88	89	88	87	86	86	86	87	96	96	—	—	—

* This reading was preceded by a period of coughing.

† Fallot's tetralogy and patent ductus arteriosus.

‡ Classified as pulmonic atresia with well developed bronchial artery collateral supply to the lungs: "pseudotruncus arteriosus."

brachial artery than in the femoral artery,[13] and a patent ductus arteriosus was demonstrated and ligated in the other (H. G.).

Results

The change in arterial oxygen saturation was calculated as an increase or decrease above or below the resting level. Normal subjects, 25 in number, showed a progressive rise in arterial oxygen saturation during maximal voluntary ventilation. The average increase was 3.5 per cent at the end of one minute, with a range of +2 to +7 per cent. The standard exercise produced very little change. An average decrease of 1 per cent was present at the end of one minute with a maximal increase of 1 per cent and a maximal decrease of 3 per cent. A further slight fall took place when exercise was stopped. The majority returned to the resting level one minute after completing the test. Oxygen administration caused an average increase of 4.5 per cent at the end of one minute. A further slight increase took place so that at the end of five minutes the average increase was 5 per cent, with a range of +3 to +8 per cent. A return to the resting level was generally achieved within five minutes of discontinuing oxygen. The normal limits are indicated by broken lines in figures 1 to 4.

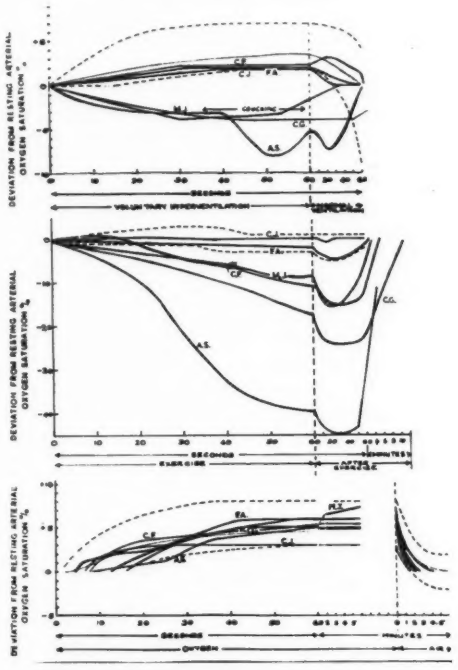

FIG. 1. Cases F. A. and C. J. had high ventricular septal defects while the remainder were those of Eisenmenger's complex. The deviation from the resting arterial oxygen saturation is shown in this and subsequent figures during voluntary hyperventilation, exercise and oxygen administration. The normal limits are shown by broken lines while the average is indicated by a faint solid line. The broken vertical line indicates the end of the test procedure. The graph was drawn from data presented in table 1 and the results are discussed in the text.

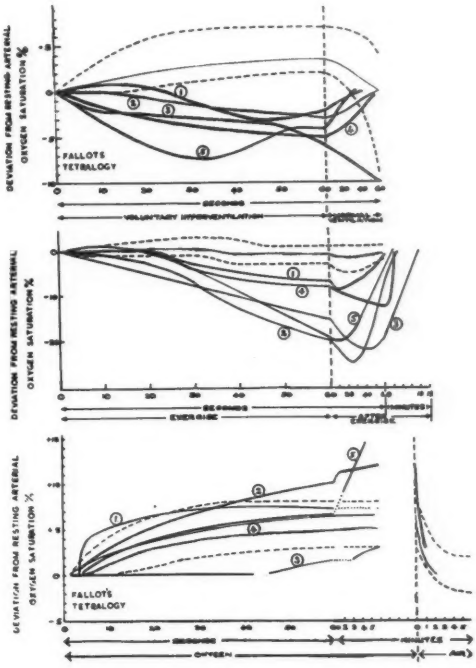

FIG. 2. The results of five cases of Fallot's tetralogy are shown. Number 1 was case R. N., number 2 case G. T., number 3 case C. W., number 4 case N. N., number 5 case S. C., table 1.

Voluntary hyperventilation, exercise and oxygen administration resulted in changes within the normal limits in cases of uncomplicated atrial septal defect. (See table 1.) Exer-

cise and oxygen administration gave a normal response in two cases of uncomplicated pulmonic stenosis. The increase in arterial saturation during hyperventilation in these cases reached the lower limits of normal at the end of one minute. (See table 1.)

Two cases (C. J. and F. A.) in the group diagnosed as high ventricular septal defect or Eisenmenger's complex showed an essentially normal response and were classified as high ventricular septal defects. The remaining cases were diagnosed as Eisenmenger's complex because of a resting or effort induced arterial unsaturation (fig. 1). One case (C. F.) had a normal resting arterial saturation and the results of voluntary hyperventilation and oxygen administration were normal. Exercise, however, produced an abnormal fall. The remaining three cases (M. J., C. G. and A. S.) showed a marked drop during hyperventilation and exercise. In case M. J. the resting saturation was within normal limits, while in the other two cases they were reduced (C. G. 83 per cent, and A. S. 79 per cent). A greater than normal average increase took place in all cases during oxygen administration and there was a tendency for the maximal saturation to be reached later than occurred normally.

Voluntary hyperventilation and exercise caused an abnormal decrease in arterial saturation in all six cases diagnosed as Fallot's tetralogy, while only two cases showed a greater than normal increase in arterial saturation during oxygen administration (fig. 2). The postexercise drop in saturation was greater than normal in all cases. The two cases (V. H. and J. S.) with pulmonary atresia and a well-developed collateral circulation to the lungs (pseudo-truncus arteriosus), had resting arterial unsaturation and an abnormal decrease during exercise (table 1). Case V. H. showed an abnormal decrease during hyperventilation which was not found in case J. S. Both showed a greater than average increase on oxygen administration.

Voluntary hyperventilation produced a slight rise (case P. B.), no change (cases T. R. and B. M.), and an initial fall and then a rise (case V. A.) in the four cases diagnosed as pulmonary

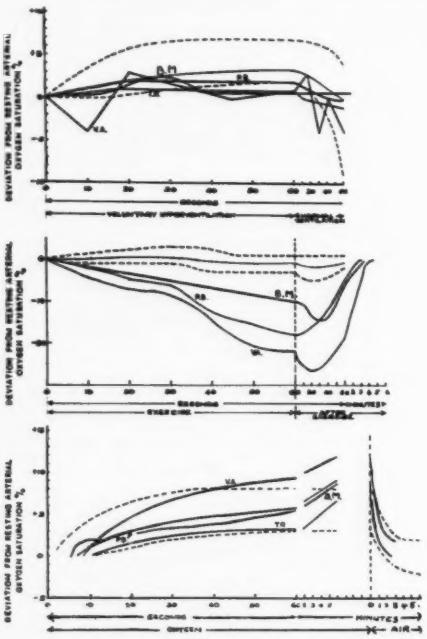

FIG. 3. Pulmonic stenosis with intact ventricular septum and patent foramen ovale.

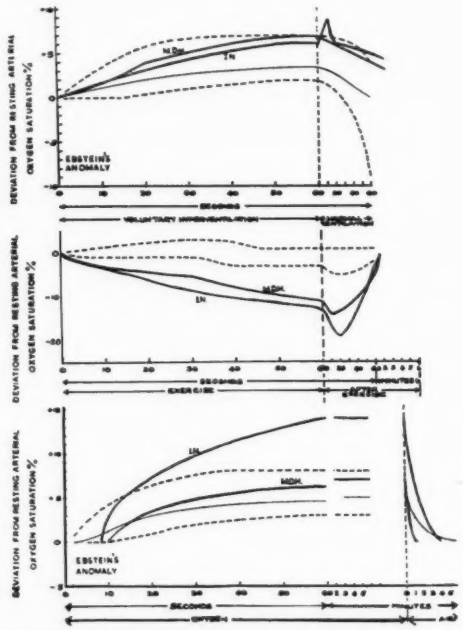

FIG. 4. Ebstein's anomaly of the tricuspid valve with patent foramen ovale.

stenosis with intact ventricular septum and patent foramin ovale (fig. 3). Exercise produced a marked drop in saturation in the three cases in which this test was performed. Two cases showed a greater than normal decrease in saturation immediately after exercise. Oxygen administration produced a greater than normal rise in three cases at the end of five minutes, and in all four cases the maximal saturation took longer to achieve than in normal subjects.

The cases of Ebstein's anomaly of the tricuspid valve associated with patent foramen ovale showed a marked increase in arterial saturation during hyperventilation (fig. 4). Exercise produced a greater than normal decrease in both. Oxygen administration produced a normal increase in one case (M. H.) and a greater than normal increase in the other (I. N.).

Partial reversal of a shunt through a patent ductus arteriosus caused resting arterial unsaturation in case D. H. and a greater than normal decrease during exercise in case H. G. (table 1). The arterial oxygen saturation of the right ear in case H. G. exceeded that in the left ear by 4 per cent, while no difference between the two ears was detected in case D. H. Whereas the fall in arterial oxygen saturation during exercise was of equal magnitude in both ears of case H. G., that in the left ear was greater than the right ear in case D. H.

Discussion

The results confirm the well documented effects of exercise and oxygen administration on the arterial blood oxygen saturation in congenital cardiac anomalies.[1–7] The presence of a venous-arterial shunt was associated with one or more of the following findings: a resting arterial oxygen unsaturation; an abnormal decrease during exercise and a further decrease immediately after exercise; an abnormally prolonged time to attain maximal saturation and failure to attain normal saturation on oxygen administration. The results of exercise, oxygen administration, and voluntary hyperventilation were within the normal limits in cases with arteriovenous shunts. This has been shown in atrial septal defects in the present study and in cases of patent ductus arteriosus and coarctation not included here. The differentiation between an arteriovenous and venous-arterial shunt can be made in the majority of cases by the changes in arterial saturation that result from exercise and oxygen administration. These tests, however, do not indicate the site of the shunt. The changes in arterial oxygen saturation during voluntary hyperventilation appeared to be of more definitive value.

A less than normal rise or an actual fall in arterial oxygen saturation during hyperventilation was found in cases with pulmonic stenosis such as Fallot's tetralogy, pulmonic stenosis with intact ventricular septum and patent foramen ovale, and isolated pulmonic stenosis. A similar result was obtained in some cases of pulmonary hypertension. With two exceptions, this occurred in the cases of Eisenmenger's complex and in one of the patients with a partial reversal of a shunt through a patent ductus arteriosus. It is likely that this result will only be obtained in pulmonary hypertension when the pulmonary resistance is relatively fixed. Under such circumstances it will limit the increase in arterial saturation in the same way as pulmonic stenosis. A less than normal increase in arterial oxygen saturation during hyperventilation was only found in the presence of pulmonic stenosis and in some cases of pulmonary hypertension, and did not occur when these conditions were absent.

In normal subjects the rise in arterial oxygen saturation during hyperventilation is due to the net effects of factors favoring the increased uptake of oxygen and the increased utilization of oxygen brought about by the effort involved in the procedure. Hyperventilation will increase the partial pressure of oxygen in the alveoli and capillary blood in the absence of lung disease. It will also increase the blood flow through the lungs by the "pumping" action of breathing.[14] The less than normal increase in arterial oxygen saturation in pulmonic stenosis and some cases of pulmonary hypertension can be ascribed to the limitations these conditions imposed on any increase in the blood flow through the lungs.

The presence of a resting arterial unsaturation in some and a greater than normal fall during exercise in all the cases diagnosed as Eisenmenger's complex, Fallot's tetralogy, pul-

monic stenosis with intact ventricular septum and patent foramen ovale, and Ebstein's anomaly with patent foramen ovale established the presence of a potential or actual venous-arterial shunt. Voluntary hyperventilation, however, produced distinctive changes. The cases with pulmonic stenosis with intact ventricular septum and patent foramen ovale showed little change from the resting arterial saturation while those with Fallot's tetralogy and Eisenmenger's complex showed a fall. This procedure appears to be of clinical value in the differentiation of pulmonic stenosis with intact ventricular septum and patent foramen ovale and Fallot's tetralogy. Eisenmenger's complex is readily distinguished from these anomalies on clinical and radiologic grounds.[9] The well marked increase in arterial oxygen saturation during hyperventilation and a fall during exercise is a distinctive finding in Ebstein's anomaly of the tricuspid valve associated with a patent foramen ovale and has not been found in any other type of cyanotic congenital heart disease.

Voluntary hyperventilation produced a fall in arterial saturation in the conditions associated with a high ventricular septal defect (Fallot's tetralogy and some cases of Eisenmenger's complex), whereas those associated with a patent foramen ovale (pulmonic stenosis with intact ventricular septum and Ebstein's anomaly) showed little change or a rise, respectively. Preliminary observations in normal subjects[14] indicate that voluntary hyperventilation lowers the total systemic peripheral resistance since it increases the cardiac output proportionately more than it increases the mean systemic blood pressure. The resistance of a stenosed pulmonic valve or lungs with marked pulmonary hypertension is likely to remain fixed. Hyperventilation in the presence of a high ventricular septal defect and pulmonic stenosis or marked pulmonary hypertension would thus favor an increase in right ventricle to aorta shunt and cause a decrease in arterial saturation. That hyperventilation does not alter the gradient of the shunt in pulmonic stenosis with intact ventricular septum and patent foramen ovale was indicated by the negligible changes that occurred in arterial saturation. The well marked increase in arterial saturation in the two cases of Ebstein's anomaly during hyperventilation was most probably indicative of a reversal of the shunt between the atria caused by a marked increase in pulmonary blood flow.

A patent foramen ovale opens from the right to the left atrium and will remain open only when the pressure in the right atrium remains higher than that in the left. Hyperventilation may increase pulmonary blood flow in Ebstein's anomaly sufficiently to raise the pressure in the left auricle and cause a partial or complete closure of the foramen ovale. A similar mechanism may operate in pulmonic stenosis with intact ventricular septum and patent foramen ovale, although any increase in blood flow will be limited by the pulmonic stenosis.

The diagnosis of Eisenmenger's complex is justified when a high ventricular septal defect and pulmonary hypertension occur in a patient with cyanosis or arterial unsaturation. The cyanosis is generally late in onset[9] and before this occurs it is extremely difficult to distinguish these cases from those with atrial septal defect by clinical means. The presence of cyanosis at rest in two of the six cases classified as Eisenmenger's complex or high ventricular septal defect made the differentiation from atrial septal defect possible. The remaining four cases showed a normal resting arterial saturation. In two of these it was possible to cause an abnormal decrease in saturation during exercise and on this basis they were separated from cases of atrial septal defect in whom the resting saturation and the change during oxygen administration, exercise and voluntary hyperventilation were normal. It is justified to consider the two cases with effort-induced unsaturation as cases of Eisenmenger's complex and to classify those in whom it did not occur as cases of high ventricular septal defect. Eisenmenger's complex is associated with dextroposition of the aorta by definition. This feature may be absent in cases of high ventricular septal defect and on these grounds it is advisable to differentiate between these conditions.

An increase in pulmonary artery pressure may occur in some cases of patent ductus arteriosus and be so great that a partial or complete reversal of the shunt results. The classic murmur of patent ductus arteriosus dis-

appears under such circumstances. In one such case Cournand and colleagues[13] have shown that the oxygen content of blood from the right brachial artery exceeded that from the femoral artery. The nature of the blood flow from pulmonary artery to aorta causes venous admixture of blood going to the femoral artery but not (or very little) to that going to the right brachial artery. Our cases demonstrate that venous blood may flow into the left carotid artery and cause the arterial saturation in the left ear to be lower than that in the right. When this difference is not present at rest it may become apparent during exercise.

The oximeter provides a means of obtaining reasonably accurate measures of the arterial oxygen saturation[8] during a variety of tests which appear to be of value in the differentiation of a number of congenital heart anomalies. Measurement of the arterial oxygen saturation at rest and during oxygen administration provides no practical difficulties. The performance of a sufficiently vigorous exercise and voluntary hyperventilation, however, necessitates cooperation and a certain degree of physical development and fitness. These latter tests can generally be performed by patients over the age of six years. The interpretation of the results from voluntary hyperventilation are only justified when the test has been performed strenuously. A better assessment of the results of this test would be to compare the changes in arterial saturation with the amount of ventilation achieved and measured as currently done for the maximum breathing capacity.[15]

Conclusions

1. An oximeter has been used to measure the changes in arterial oxygen saturation during voluntary hyperventilation, exercise and oxygen administration in 25 normal subjects and 30 cases of congenital heart disease.

2. The nature of the congenital heart anomaly was established by clinical study and venous catheterization of the heart in the majority of cases. The congenital heart anomalies studied consisted of the following types with the number in each group in parentheses: atrial septal defect (5); high ventricular septal defect (2); Eisenmenger's complex (4); isolated pulmonic stenosis without septal defects (2); Fallot's tetralogy and variants (8); pulmonic stenosis with intact ventricular septum and patent foramen ovale (4); Ebstein's anomaly of the tricuspid valve with patent foramen ovale (2); Patent ductus arteriosus with partial reversal of shunt (2).

3. Congenital heart disease associated with an arteriovenous shunt was characterized by an essentially normal response. This was found to be true for cases of atrial septal defect described in the present study and cases of uncomplicated patent ductus arteriosus and coarctation not included in this report.

4. Congenital heart disease associated with a venous-arterial shunt showed one or more of the following results: A resting arterial oxygen unsaturation; an abnormal reduction in saturation during exercise; an abnormally prolonged time to attain maximal saturation, and a failure to attain full saturation on oxygen administration. Although these findings indicate the presence of a venous-arterial shunt, they do not indicate the site of the shunt.

5. The effect of voluntary hyperventilation depended upon the presence or absence of pulmonic stenosis or pulmonary hypertension and the site of the venous-arterial shunt. A less than normal increase in arterial oxygen saturation was found in cases of pulmonic stenosis and in some cases with marked pulmonary hypertension irrespective of the associated abnormalities. This was attributed to a failure to increase pulmonary blood flow during this maneuver. Pulmonic stenosis with intact ventricular septum and a patent foramen ovale was found to produce little change in saturation during hyperventilation, whereas high ventricular septal defects in association with pulmonic stenosis (Fallot's tetralogy) or pulmonary hypertension (Eisenmenger's complex) resulted in a distinct fall. The response to voluntary hyperventilation would appear to offer a means of distinguishing a patent foramen ovale and a high ventricular septal defect when these conditions are associated with pulmonic stenosis or pulmonary hypertension.

6. A marked fall in arterial saturation during exercise was found in two cases of Ebstein's anomaly of the tricuspid valve and patent

foramen ovale, but unlike other types of cyanotic congenital heart disease, there was a normal response during hyperventilation.

7. The possible mechanisms of these different responses during voluntary hyperventilation have been discussed, and it is suggested that this procedure may be of differential diagnostic value in the study of congenital heart disease.

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The Effect of Age and Body Weight on the Electrocardiogram of Healthy Men

By Ernst Simonson, M.D., and Ancel Keys, Ph.D.

It is believed that proper evaluation of the electrocardiogram of a patient should mean comparison with the electrocardiographic features in healthy individuals who are in other respects comparable. Among the "other respects," age and body weight are important constitutional variables. The present information about the effect of these factors on the electrocardiogram is not adequate and, therefore, the differentiation between normal and abnormal is less precise than need be. In this paper, information is provided on the effect of age and body weight on the electrocardiogram, on the basis of a statistical analysis of various electrocardiographic items in numerically adequate samples of normal male population. It is shown that the effect of both age and weight is statistically highly significant, so that their consideration in electrocardiographic normal standards is suggested.

A MAJOR purpose of recording electrocardiograms in clinical practice is to aid in the classification of the health-disease status of the individual with a view to diagnosis and prognosis. Though current, conventional electrocardiography has shortcomings in its applications to manifest disease, the status of this aspect is relatively satisfactory compared with the situation in the borderline between health and disease and in the prediction of departures from present health.

The stock phrase, "within normal limits," presumably means that the electrocardiogram conforms to the expectation in the absence of demonstrable disease. However, the "normal limits" cover a wide range of voltages, time intervals and patterns and these are not haphazard; the records dismissed with this designation are individually different and are characteristic of individuals. It is scarcely credible that all of these representations in the "normal range" are of equal significance, or lack of significance. Nor is it reasonable to suppose that the expectations, which are defined by the normal limits, should be the same for both sexes, all ages and all metabolic patterns.

One approach to a sharpened focus on these questions is to compare the electrocardiographic characteristics of several categories of healthy people, with a view to a better definition of norms for these categories. Consider a slender young man and a fat middle-aged man, both clinically healthy in the usual sense. Are the standards of electrocardiographic expectation the same for both? Some awareness of this problem is expressed in textbooks on electrocardiography but no quantitative answers have been forthcoming. On the principle that any finding on a patient should be compared with the characteristics of healthy people who are otherwise comparable, we have set out to discover whether such factors as age and relative obesity should be considered.

Until now, the only electrocardiographic items in which a normal trend with age has been recognized are those which relate to the electrical heart position: QRS axis,[1, 2] heart index,[3, 4] and the position indicated by the unipolar limb leads.[5] But even with these items the reported age trends are inadequate to establish norms because of lack of definition of other characteristics (for example, body build and relative obesity), as well as the lack of satisfactory statistical analysis.

In regard to the effect of body weight, it is well known that overweight tends to be associated with a left axis shift and that underweight persons tend to show right axis deviation. These tendencies are usually explained in terms of mechanical changes in the heart position but they have not been systematically studied or analyzed statistically. Schlomka[3] studied the electrical heart position in obesity, but

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most of his subjects had hypertension and he did not study underweight persons. Other features of the electrocardiogram have received even less attention in regard to possible relationships to the relative obesity or emaciation of the subject.

The present paper reports studies on healthy young and middle-aged men with the limb leads, both bipolar and unipolar, and with CF_4.

Subjects

The subjects comprised 157 men between 18 and 25 years of age and 233 men between 45 and 55 years of age. All of these men were judged to be entirely healthy and "normal" from detailed clinical and laboratory examinations on the day of the electrocardiographic study and absence of any physical complaints. Besides the usual points of examination, these men received special tests, including standard exercise on the motor-driven treadmill (15 minutes of walking at 3 miles per hour on the horizontal), the cold pressor test, the carbon dioxide inhalation test (6 per cent carbon dioxide for five minutes) and a reactive hyperemia test (optical plethysmographic recording of the great toe before and following five minutes of complete occlusion of the circulation in the leg).

The men were selected from a larger group to give adequate numbers of fat and thin men, that is, the group as a whole was not a random sample in regard to obesity-emaciation.

The two age groups were each subdivided into five weight groups (A to E), with reference to the standard weight, expected from height and age, as indicated in the standards of the medico-actuarial Mortality Investigations[6] which are generally used in the United States. The weight ranges of these groups, as percentages of the standard weight, were, for groups A to E in order: 85 per cent or less, 86 to 95, 96 to 105, 106 to 115, and over 115 per cent. The weight data are summarized in table 1. In the two age groups the differences between the mean relative weight of the extreme groups (A and E), were almost identical (young men 43.0, middle-aged men 44.1 per cent of the standard weight for height and age).

Methods

All electrocardiograms were recorded in basal rest in a quiet, controlled environment room (77 F., humidity 50 per cent relative saturation). Besides the bipolar, unipolar limb leads and CF_4, recordings were made of the chest leads V_1, V_2, V_4, and V_5. The latter were useful in assuring the normality of the subjects.

In the standard limb leads the following items were measured: *Intervals* R-R, Q-T, P-R, and QRS, *amplitudes* P_2, QRS, T, S-T segment, Σ_{QRS}, and Σ_T, *axes* QRS and T, an arrhythmia index (ΔR-R, the difference between the longest and the shortest R-R intervals in a given record), and the quotient K_{Q-T} (Q-T divided by square root of R-R).

For the analysis of the unipolar limb leads the electrocardiograms were classified in groups with regard to the electrical position of the heart, using the criteria of Wilson and his co-workers,[7] as: horizontal (H), semihorizontal (SH), intermediate (I), semivertical (SV) and vertical (V). Several cases with rather extreme clockwise rotation and one case of dextrocardia (*situs inversus*) were excluded. For each of these positional groups in each of the three leads V_R, V_L, V_F, the following items were measured: QRS interval, Q-R (time from the start of the ventricular complex to the peak of the intrinsicoid deflection) and the amplitudes of P, Q, R, S, S-T segment and T.

Standard statistical methods were used to characterize the several sets of data. The significance of the differences between means was estimated by the *t* and the *F* tests. If this difference proved significant, then the regression of the characteristic or relative weight for the five weight groups, and the significance of the slope of the regression line, were calculated.

Table 1.—*Mean Values for Body Weight, Height and Percentage of Standard Weight for Height and Age in 157 Healthy Young Men (18 to 25 Years) and 222 Healthy Middle-aged Men (45 to 55 Years) Grouped According to the Percentage of Standard Weight (A ≦ 85, B = 86 to 95, C = 96 to 105, D = 106 to 115, E > 115)*

Group	Young Men					Middle-aged Men				
	A	B	C	D	E	A	B	C	D	E
Number	12	36	49	30	30	39	49	66	42	26
Weight, Kg.	55.5	64.7	71.7	78.2	88.7	60.6	67.5	75.9	82.2	91.5
Height, cm.	176.9	176.9	175.4	175.2	174.7	173.0	177.6	178.4	177.0	176.0
% Standard Wt.	81.2	90.8	99.4	110.1	124.2	78.2	90.0	100.0	108.8	122.3

I. Effect of Age

Results—Standard Limb Leads and CF_4

Table 2 summarizes the findings in the standard limb leads and CF_4. The QRS and Q-T intervals and the amplitudes of P_2, Q and of the S-T segment failed to show significant age differences but the great majority of the items measured showed differences between the as of the mean values. In every instance it was found that the median values showed substantially the same age differences as exhibited by the means. This indicates that there are consistent differences between the two age groups and that these are well represented by the differences between the means.

Since both age groups contained both fat and lean men as well as men of normal weight, it

Table 2.—*Standard Limb Leads and CF_4 in 157 Young Men (Y) and in 233 Middle-aged Men (O). Means (M) and Standard Deviations (s.d.), Differences Between the Means (ΔM) and the t Values for the Differences. For the 0.01 Level of Significance t = 2.62; for the 0.001 Level t = 3.37. For Comparison, the Means and Standard Deviations Are Given for 1000 Young Aviators (G) Studied by Graybiel and Co-workers.[8] All Amplitudes in Standardized mm. (1 mm. = 0.1 Millivolt), Intervals in 1/100 Second, Axes in Degrees*

Group	Mean s.d., t	P_2	R_1	R_2	R_3	S_1	S_2	S_3	T_1	T_2	T_3	T-CF_4
Y	M	0.96	4.87	11.61	7.88	−1.27	−1.12	−0.79	2.46	3.21	0.89	6.38
Y	s.d.	0.46	2.42	3.63	4.35	1.09	1.23	1.17	0.91	1.13	1.22	2.64
O	M	0.88	6.09	7.75	3.54	−0.74	−0.78	−1.65	2.01	2.26	0.22	5.18
O	s.d.	0.35	2.63	3.16	3.29	0.97	0.98	2.15	0.89	0.95	1.14	2.13
O–Y	ΔM	−0.08	1.22	−3.86	−4.34	0.53	0.34	−0.86	−0.45	−0.95	−0.67	−1.20
	t	1.9	4.0	10.8	10.6	4.9	2.9	5.1	4.8	8.6	5.3	4.7
G	M		5.90	11.60	7.10				2.50	3.30	1.20	
G	s.d.		2.57	3.88	4.20				0.88	1.18	1.19	

Group	Mean s.d., t	$\angle_{QRS}$	$\angle_T$	QRS Axis	T Axis	Intervals				
						P-R	R-R	QRS	ΔR-R	K_{Q-T}
Y	M	29.05	7.05	66.75	42.78	15.24	97.60	8.44	11.64	0.388
Y	s.d.	8.39	2.75	21.32	21.74	1.90	17.53	0.16	10.62	0.027
O	M	21.51	5.20	37.77	32.87	15.91	96.00	8.46	6.50	0.398
O	s.d.	6.36	1.74	34.67	23.26	2.13	13.51	0.14	4.36	0.022
O–Y	ΔM	−7.54	−1.85	−28.98	−9.91	0.67	−1.60	0.02	−5.14	0.01
	t	9.5	7.5	10.2	4.3	3.2	1.00	0.6	8.1	0.4
G	M			64.2						
G	s.d.			23.3						

young and the middle-aged men which were statistically highly significant.

Comparison of the two age groups by these statistical methods is valid only if the frequency distributions of the several items are similar in the two groups or, better, if they are not far from Gaussian (corresponding to the normal probability curve). This question was examined by making comparisons of the medians as well could be suggested that the observed age trend might be related to differences in the frequency of relative obesity and emaciation in the two groups. This seemed unlikely since the distribution of relative body weights was similar in the two age groups. However, to eliminate this question, and to get an indication of the variations related to variations in relative obesity, a separate analysis was made in which were

TABLE 3.—*Standard Limb Leads and CF_4 in 49 Young Men (Y^1), and 66 Middle-aged Men (O^1) All of Whom Were Within ± 5 Per Cent of the Standard Body Weight for Height and Age. Means (M) and Standard Deviations (s.d.), Differences between the Means (ΔM), and t Values. For the 0.05 Level of Significance, t = 2.00, for the 0.01 level, t = 2.66*

Group	Mean s.d., t	R_1	R_2	R_3	S_1	S_2	S_3	Σ_{QRS}	Axis
Y^1	M.	4.82	11.97	8.08	−1.29	−1.17	−0.79	29.64	66.43
	s.d.	2.20	3.46	3.91	1.08	1.13	1.17	8.83	23.07
O^1	M.	7.01	7.58	2.99	−0.73	−0.65	−1.91	21.56	34.72
	s.d.	2.54	2.96	2.58	0.93	0.97	2.48	5.19	9.28
	ΔM	+2.19	−4.39	−5.09	+0.56	+0.52	−1.12	−8.08	−31.71
	t	4.9	7.1	7.9	3.1	2.6	3.2	5.7	9.1

Group	Mean s.d., t	T_1	T_2	T_3	ΣT	T-CF_4	Axis	P-R	K_{Q-T}	ΔR-R
Y^1	M.	2.48	3.35	0.92	7.07	7.12	43.06	14.90	.385	11.30
	s.d.	0.758	1.09	0.95	1.87	3.38	15.99	2.01	.0231	3.26
O^1	M.	2.30	2.11	−0.11	5.20	5.23	24.09	16.09	.395	6.06
	s.d.	0.760	0.83	0.998	1.64	1.62	18.20	2.25	.0221	4.17
	ΔM	−0.18	−1.24	−1.03	−1.87	−1.89	−18.95	+1.19	0.01	−5.24
	t	1.3	6.6	5.6	5.6	3.6	5.9	2.9	2.4	7.5

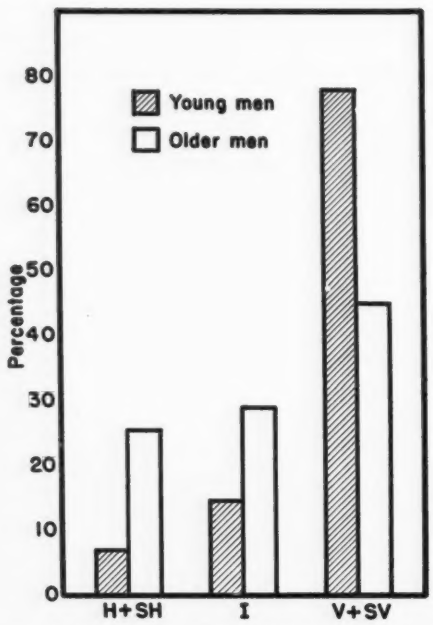

FIG. 1. Distribution of electrical heart positions as estimated from unipolar leads in 157 young and 233 middle-aged men.

included only men within ±5 per cent of standard weight for height and age. The results with these 115 men were very similar to those shown in table 2 and showed clearly that the differences between young and middle-aged men are not the results of differences in the samples in regard to relative obesity.

Comparison of table 3 with table 2 shows that restricting the range of relative obesity has the effect of reducing the variation, indicated by the standard deviations, in many of the electrocardiographic characteristics. This points to the need for considering relative obesity in formulating standards; this question will be examined in greater detail in part II.

Results—Heart Position

Table 4 shows the frequency of the five heart positions in the two age groups. However, the five positional groups are not equivalent in respect to local representation of the electrocardiographic patterns; septum potentials can be found only over comparatively narrow zones and this limits the number of individuals with positions SH and SV. A clearer picture of the difference in the distribution of heart positions is provided by combining the H and SH and the V and SV groups as shown in figure 1. The vertical and semivertical heart positions are most common in both age groups but the

younger men tend to have considerably more vertical hearts and only about 7 per cent of the young men have heart positions that can be classed as horizontal or semihorizontal. However, the H or SH position is not so rare in perfectly healthy young men as to justify fully the conclusion of Sokolow and Fiie llander[5]: "A horizontal heart in a young individual should raise doubts of normality."

Results—Intervals and Amplitudes in the Unipolar Limb Leads

The significant findings in the unipolar limb leads are summarized in tables 5 (H + SH), 6 (I) and 7 (V + SV). In all of these heart positions there were highly significant differences of the mean QR or QRS intervals in middle-aged men as compared with young men, the intervals being shorter in the older men. Highly significant age trends of amplitudes (voltages) were also observed in all of these heart positions.

It will be noted that the age trends of V_L and V_F in amplitude in the intermediate heart position (table 6) are less pronounced than in the other heart positions. In V_L in the intermediate heart position there was no statistically significant amplitude change with age, and in V_F only the S amplitude showed a significant difference. It should be recalled, however, that in the intermediate heart position potentials of the left ventricular epicardial surface are projected both to V_L and V_F, the projection varying with the position of the heart within the group. This must add considerably to the total variability of amplitudes in V_L and V_F in the intermediate position and age trends would be correspondingly more difficult to demonstrate. It is relevant to this argument that the incidence of significant age trends in V_R is about the same in all three positional groups. Positional variability is least in V_R.

The general age trend in QRS and T amplitudes is toward a decrease in all heart positions in all three unipolar limb leads. The results confirm and increase the significance of the findings with the standard (Einthoven) limb leads. Since the age trends were observed in groups of men with similar heart positions, they must be due in large part to changes independent of positional shift with age.

As in the case of the standard limb leads, it seemed desirable to make sure that the results were not influenced by possible differences between the two age groups in the frequency distribution of relative obesity. In the positional group V + SV there were enough men of both ages within ±5 per cent of standard weight for height and age to examine this question. The results were not different from those presented above for the full groups of men and we may be confident that no extrane-

TABLE 4.—*Frequency Distribution, in 114 Young Men (Y) and 202 Middle-aged Men (O) of the Heart Position Classed in the Positional Groups: Horizontal (H), Semihorizontal (SH), Intermediate (I), Semivertical (SV), and Vertical (V). For Each Group is Also Shown the Mean Axis (Axis) and its Standard Deviation (s.d.), the Difference in the Axis Means Between the O and Y Groups, and the F Values of those Differences*

Group	Item	H	SH	I	SV	V	H + SH	V + SV
Y	No.	8	0	17	6	83	8	89
Y	%	7.0	—	14.9	5.3	72.8	7	78.1
Y	axis	19.5	—	39.9	58.7	74.7	19.5	73.6
Y	s.d.	32.0	—	15.6	14.2	11.1	32.0	12.0
O	No.	34	18	59	29	62	52	91
O	%	16.8	8.9	29.2	14.4	30.7	25.7	45.1
O	axis	6.4	10.7	41.9	64.8	69.4	7.9	67.9
O	s.d.	16.1	14.9	15.8	16.0	13.2	15.7	14.2
O–Y	axis	−13.1	—	+2.0	−6.1	−5.3	−11.6	−5.7
O–Y	axis, F			0.21			2.77	8.39

F for H + SH p0.05 = 4.00.
F for V + SV p0.01 = 6.82.

ous influence of the frequency distribution of relative fatness was present in the original analysis.

acteristic for which definite age trends have been recognized. The present results are fully confirmatory both in the standard limb leads

TABLE 5.—*Statistically Significant Differences between Young (Y) and Middle-aged (O) Men in Unipolar Limb Leads. Horizontal and Semihorizontal Hearts. For the 0.05 Level of Significance,* F = *4.00; for the 0.01 level,* F = *7.08*

Age, No.	Item	Lead V_R					Lead V_L		
		Interval		Amplitude			Interval		Amplitude
		Q-R	QRS	R	QS	S-T	Q-R	QRS	Q
Y (8)	M.	6.86	9.63	1.04	−5.61	−0.36	5.00	9.75	−0.78
Y (8)	s.d.	1.07	1.06	0.60	2.09	0.45	0.53	1.39	0.29
O (52)	M.	5.60	7.39	0.33	−4.22	−0.06	4.10	8.46	−0.29
O (52)	s.d.	0.88	1.11	0.39	1.41	0.18	0.77	1.45	0.18
	Δ	−1.26	−2.24	−0.71	−1.39	+0.30	−0.90	−1.29	−0.49
	F	11.08	28.65	20.10	5.91	12.12	10.11	5.54	15.04

Age, No.	Item	Lead V_F				
		Interval	Amplitude			
		QRS	Q	R	S	S-T
Y (8)	M.	9.38	0.0	2.06	−1.79	0.10
Y (8)	s.d.	1.51	0.0	1.87	0.90	0.19
O (52)	M.	7.87	−0.02	0.95	−0.86	−0.04
O (52)	s.d.	1.53	.066	0.59	0.76	0.14
	Δ	−1.49	+0.02	−1.11	−0.93	−0.14
	F	6.65	6.74	11.87	9.84	6.70

TABLE 6.—*Statistically Significant Differences between Young (Y) and Middle-aged (O) Men in Unipolar Limb Leads. Hearts of Intermediate Position. For the 0.05 Level of Significance,* F = *3.98; for the 0.01 level,* F = *7.01*

Age, No.	Item	Interval QRS	Lead V_R Amplitudes				Lead V_L Interval QRS	Lead V_F Amplitude S
			R	QS	T	S-T		
Y (17)	M.	8.53	0.53	−5.82	−2.22	−0.40	8.47	−0.51
Y (17)	s.d.	1.01	0.48	1.84	0.66	0.25	1.12	0.54
O (59)	M.	7.61	0.30	−4.07	−1.46	−0.10	7.41	−0.21
O (59)	s.d.	1.51	0.31	1.51	0.64	0.19	1.56	0.40
	Δ	−0.92	−0.23	−1.75	−0.76	+0.30	−1.06	−0.31
	F	5.57	5.73	16.01	18.26	28.27	6.90	6.06

Results—The QRS Axis

In the introduction to this paper it was remarked that until now the electrical heart position was the only electrocardiographic char-

and in the unipolar leads. It may be remarked that even when the comparisons are restricted to the same positional type, the young men had more vertical hearts, as estimated by the

QRS axis, than their older counterparts. This would be expected when a quantitative measure (QRS axis) is applied to semiquantitative groupings, as in the unipolar positional scheme, if there is a general tendency to verticality throughout the young men.

Comment

It is important to consider the extent to which the present data may have general applicability beyond the local population sampled here. As shown in table 2, the data on the present group of young men correspond closely for the limb leads with the data from the series of 1000 young aviators studied by Graybiel and his associates.[8] Comparable data for CF_4 and the unipolar limb leads are not available. Unfortunately, there are in the literature no comparable data on a large sample of older men.

The determination of the normality of the men studied here was carefully made but it was limited by present-day diagnostic procedures. It is known that there is a high incidence of myocardial lesions which are not diagnosed during life, especially in older people,[9–11] and this is sometimes true even for advanced myocardial damage. It must be assumed, therefore, that the present sample, especially the older age group, includes a certain proportion of individuals with undetected minor, or perhaps even major lesions. The age trends observed here were, in general, in the direction of electrocardiographic abnormality (low voltage, left ventricular strain); the trends may, therefore, be the result or may be indications of progressive, degenerative myocardial changes.

TABLE 7.—*Statistically Significant Differences between Young (Y) and Middle-aged (O) Men in Unipolar Limb Leads. Vertical and Semivertical Hearts. For the 0.05 Level of Significance, F = 3.91; for the 0.01 level, F = 6.82*

Age, No.	Item	Interval		Lead V_R Amplitudes			
		Q-R	QRS	P	QS	T	S-T
Y (52)	M.	6.52	8.84	−0.52	−6.27	−2.41	−0.29
Y (52)	s.d.	1.21	1.31	0.22	1.95	0.76	0.25
O (91)	M.	5.77	8.07	−0.45	−4.06	−1.55	−0.08
O (91)	s.d.	1.16	1.47	0.23	1.72	0.64	0.20
	Δ	−0.75	−0.77	−0.07	−2.19	−0.86	+0.19
	F	11.19	13.82	3.86	64.76	67.64	36.00
		Lead V_L		Lead V_F			
		Interval QRS	Amplitude S	Interval QRS	Amplitude P	Amplitude R	Amplitude S
Y (52)	M.	9.11	−3.29	8.96	0.38	6.16	−0.45
Y (52)	s.d.	1.76	2.07	1.35	0.28	2.57	0.48
O (91)	M.	7.71	−1.47	8.35	0.54	4.98	−0.26
O (91)	s.d.	1.79	1.54	1.45	0.37	2.49	0.44
	Δ	−1.40	−1.82	−0.61	+0.16	−1.18	−0.19
	F	27.87	45.39	8.27	13.44	9.80	7.51

The current clinical custom in electrocardiography is to refer to "limits of normality," without regard for age. Though we have considerable doubt as to the meaning or validity of such limits, it is of interest to apply them to the present subjects who were unusually well screened in regard to clinical health. With the usually accepted limits for P-R (= 0.21 second) low voltage (Σ_{QRS} = 15.0 mm.), Q_3 (25 per cent of largest R in leads 1 to 3), and S-T depression (−0.5 mm. in leads I and II), the percentages of the younger and older men, respectively,

outside of these limits were: P-R, 0.6 and 3.4; Σ_{QRS}, 6.4 and 11.2; Q_3, 3.2 and 9.0; S-T depression, 2.5 and 7.3. Similar proportions were found with other screening levels; in all cases the percentage of "abnormal" findings was several times as high in the middle-aged men as in the young men.

It scarcely seems justifiable to consider that a finding which appears in 5 or 10 per cent of such carefully screened middle-aged men is to be labeled "abnormal." On the other hand, it is safe to predict that many of these healthy middle-aged men will eventually develop heart disease. And it is not unreasonable to suggest that there might be a correlation between the development of cardiac disease and the departure of the present electrocardiograms from the limits found in healthy young men. This is, however, conjectural at present and not a valid argument for dismissing what must be considered normal age trends. In dealing with middle-aged men we must compare them with other middle-aged men and standards for this purpose seem essential. Until long-range follow-up studies are completed, there is no basis for judging the prognostic significance of particular electrocardiographic findings which are relatively common in healthy men, even though some of these findings are very rare in men in the twenties.

The present study of age trends is confined to young and middle-aged men and it is rash to infer from these that the trends from young manhood to the period from 45 to 55 years of age may be extrapolated at either end of this age range or, for that matter, that there is a smooth and regular transition between these ages. Nevertheless, there is some basis for judgment about the electrocardiographic characteristics at these other ages.

In old age it appears that the application of standards derived from studies on young people shows a very high incidence of "abnormalities," even when the old subjects are screened to eliminate all persons who, clinically, are not in good health. Feldman and co-workers[12] found definitely "abnormal" electrocardiograms in 30 out of 45 clinically healthy persons over 80 years of age. This would seem to indicate a continuation and extension of the trend observed here; it re-emphasizes the need for more precise definitions of "normality."

Recently there have been published several valuable studies on the electrocardiogram in children.[13–15] These are mainly concerned with young children and in no case provide any information beyond the age of 15. There is an important gap, then, between these ages and the young men reported here. However, it may be remarked that in some respects the differences between children and young men are in the same direction as the differences reported here between young and middle-aged men. The electrical axis of the heart tends to be more vertical, the total voltages of R and of T tend to be higher, and the P-R interval tends to be less, in children than in young adults. In these items there is evidence for a continuous and progressive trend with age from childhood to middle-age at least.

II. Effect of Body Weight

In part I, the effect of body weight in the analysis of age trends was canceled out or minimized by comparing total groups of similar weight distribution or partial groups with identical standard weight. This does not mean, of course, that there are no weight trends; on the contrary, the smaller standard deviation in the partial weight groups, compared to the total groups, suggests that relative fatness is another factor besides age which influences the electrocardiogram.

Results—Standard Limb Leads and CF_4

Table 8 summarizes the findings with the standard limb leads and CF_4 for all items in which a plot of the mean values for the several weight groups suggested a continuous trend.

The number of items with a significant weight trend is smaller in the young men than the older men. In part, at least, this may be merely a reflection of the fact that the groups of young men contained fewer individuals and hence statistical significance is more difficult to establish; it was unfortunate that there were only 12 very thin (group A) young men. However, there are indications that relative differences in fatness in a young man may actually have less effect on the electrocardiogram than

similar differences in fatness in middle-aged men. In table 8 the mean differences (Δ) between groups A and E are smaller for the young men than for the older men.

With the exceptions of items in which the error of measurement is large compared with the measurement itself (for example amplitudes of Q, S_1, and S-T segments, not included in table 8), practically all amplitudes show significant differences between fat and thin men. The highly significant differences in the QRS and T axes are, of course, not unexpected. But none of the intervals shows a relationship to relative body weight.

A few of these items proved to show no statistically significant difference between weight groups A and E (last five lines in table 8). It does not follow that these items, or others not listed in table 8, do not actually discriminate between thin and fat men. It can merely be stated that the present data do not prove such discrimination.

The high significance of the slopes (b) in table 8 proves that the best (least squares) straight line fitted to the means of the five weight groups is significantly different from the horizontal. However, this should not be taken to mean necessarily that the trend is primarily linear. Examination of the data in graphic form suggests, indeed, that the real trend is curvilinear in some items. Figures 2 and 3 indicate the situation for the voltages R_2 and T_1. In most items, however, it seems that the data are reasonably well fitted by a linear equation of the type $y = a + bx$, where y is the electrocardiographic item of measurement, and x is the relative body weight.

In a few electrocardiographic items it was possible to show, with statistical significance, that maximum or minimum mean values occurred at other than the ends of the relative weight distribution. Several of these are summarized in table 9. In young men, for example, the voltage in lead II (R_2) was significantly

TABLE 8.—*Means and Standard Deviations of Electrocardiographic Items in Thin (Group A) and Fat (Group E) Men, the Differences (Δ) between These Means, and the Slope (b) of the Regression Line for All Five Relative Weight Groups. Y Indicates Young Men, O Indicates Middle-aged Men. Amplitudes in Standardized mm. (1 mm. = 0.1 mv.), Intervals in 1/100 Second, Axis in Degrees. Statistical Significance is Indicated by Asterisks:* * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$

Age	Item	Group A		Group E		Δ	b (Slope)
		Mean	s.d.	Mean	s.d.		
Y	R_1	3.80	1.82	6.55	3.08	2.75**	0.053***
Y	T_1	1.49	0.97	2.89	0.98	1.40***	0.022***
Y	T_3	1.84	1.08	0.31	1.25	−1.53***	−0.033***
Y	T axis	62.00	10.88	31.87	21.77	−30.13***	−0.576***
O	R_1	3.86	2.41	7.44	2.57	3.58***	0.090***
O	R_2	8.95	3.24	6.59	2.47	−2.36**	−0.065***
O	R_3	5.49	3.13	2.21	2.73	−3.28***	−0.099***
O	S_3	−1.00	1.78	−2.00	2.13	−1.00*	—
O	T_2	2.80	0.88	1.65	0.76	−1.15***	−0.029***
O	T_3	1.03	1.01	−0.63	0.66	−1.66	−0.041***
O	Σ_T	5.74	1.69	4.55	1.52	−1.19**	−0.032***
O	QRS axis	61.61	24.24	31.42	8.06	−30.19***	−0.787***
O	T axis	51.77	17.50	11.12	19.15	−40.65***	−0.941***
O	CF_4-R	6.92	5.14	10.82	5.34	3.91**	0.085*
O	CF_4-T	5.99	2.22	4.03	1.50	−1.96***	−0.036*
O	CF_4-R/S	1.05	1.94	2.17	1.80	− 1.12*	—
Y	T_2	3.44	1.04	3.04	1.08	−0.40	—
Y	QRS axis	70.30	19.45	59.80	20.70	−10.50	—
Y	ΔR-R	10.50	4.74	12.50	12.01	2.00	—
Y	QRS int.	8.33	0.89	8.67	1.73	0.34	—
O	S_2	0.95	1.05	0.66	0.606	−0.29	—

higher in the B group (moderately thin men) than in either the A or the E groups (very thin and very fat men). It is interesting that these trends may be different at the two different ages; R_2 is a good example. R_2 shows a continuous trend in middle-aged men, becoming progressively smaller with increasing relative body weight, with no sign of an intermediate maximum, such as seen in the younger men. (Compare fig. 2.)

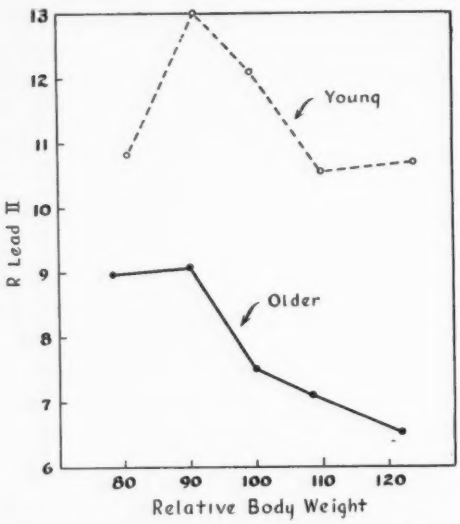

FIG. 2. Differences in the weight trend of R_2 in young men and middle-aged men. This is a statistically significant maximum in weight group "B" of the young men, while in the older men R_2 is identical for weight groups A and B, and declines consistently for the heavier weight groups C to E.

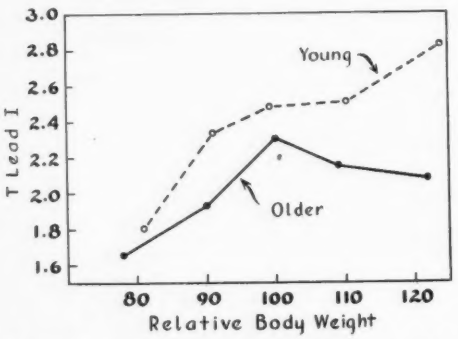

FIG. 3. T_1 shows a maximum for the normal weight group (C) of older men, but a continuous increase with weight in the young men.

Results—Unipolar Limb Leads

For the analysis of the relationships in the characteristics obtained with the unipolar limb leads it was necessary to consider the electrical position of the heart. For statistical reasons, the vertical (V) and semivertical (SV) positions and the horizontal (H) and semihorizontal (SH) positions were combined so the analysis was carried out with three classifications: H + SH, I, V + SV.

The distribution of the subjects in this three-category classification was determined for each of the relative weight groups for both ages. The results, in which the occurrence of the three heart positions in each weight group are expressed as a percentage of all men in the weight group, are summarized in figure 4. It should be noted that some of the groups were very small, so the reliability is not the same in all parts of figure 4. For example, there were only seven young men in body weight group A and they all had vertical or semivertical hearts. Conceivably, some healthy young men who are very thin might have hearts in the intermediate or horizontal position but none appeared in the present series. Also, it is important that horizontal and semihorizontal hearts are uncommon in all healthy young men so no great reliance can be given to the particular percentages in the several weight groups found here and depicted in figure 4. The larger numbers of men with vertical or semivertical hearts produce a more favorable situation to show reliable trends.

For calculation of the effects of relative obesity-emaciation, the principal analysis was carried out, in the two ages separately, by comparing the thin (groups A and B) with the fat (groups D and E) men, the strictly "medium" men (group C) being discarded. Even so the numbers of young men with hearts in positions I and H + SH were too small for useful comparison.

Table 10 summarizes the data from unipolar limb leads in which significant differences were found between fatter and thinner men. It will

be noted that no significant differences were found in lead V_R.

Comment

It is clear from these data that, in healthy men, differences in relative fatness or leanness are reflected in characteristic differences in the electrocardiograms and that these differences are not confined to those items which are influenced by heart position. Moreover, some distinction must be made between the anatomic heart position and the electrical axis or electrical heart position. The relative masses of the right and left ventricles, as well as the geometric position of the whole heart, are involved in the electrical axis and position.

Schlomka[3] concluded that the shift to the left of the electrical position of the heart in obesity cannot be explained by anatomic position alone. Schlomka observed the electrical shift in the compensated condition but not in uncompensated heart disease, although the anatomic position, as observed by roentgenography, was not altered in decompensation. Schlomka and Witsch[16] also reported a prolonged Q-T interval, as calculated by Fridericia's formula, in 196 older persons who were overweight. Most of their subjects had an elevated blood pressure, which may account for the difference from the present series in which there was no significant relationship between relative body weight and K_{Q-T}.

At present, V_4 is more commonly taken than CF_4 but it is believed that the trends reported here for CF_4 would be reflected also in V_4.

The interaction between age and relative body weight is interesting. It will have been noticed that the relationships between relative body weight and electrocardiographic characteristics are not identical in the two age groups of men studied here. In many items the effect of relative body weight seems more pronounced in the older men and it might be suggested that both increasing weight and age involve similar mechanisms of effect on the electrocardiogram. However, the parallelism is by no means exact, as inspection of table 8 and figures 2 to 4 will show.

TABLE 9.—*Significant Maxima or Minima in Electrocardiographic Weight Trends. Y = Young Men, O = Middle-aged Men. Levels of Significance* * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

Item	Age Group	Weight Group A		Weight Group E		Weight Group	Max. or Min.		Differences	
		Mean	s.d.	Mean	s.d.		Mean	s.d.	8–3	8–5
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
R-R int.	Y	94.9	10.12	103.6	19.10	B	86.9	13.24	8.0*	16.7***
R_2	Y	10.88	3.15	10.66	2.71	B	13.01	1.44	2.13*	2.35***
R_3	Y	8.02	4.37	5.95	3.34	B	9.93	5.28	1.91	3.98**
T_1	O	1.66	0.83	2.09	0.74	C	2.30	0.76	0.64**	0.21

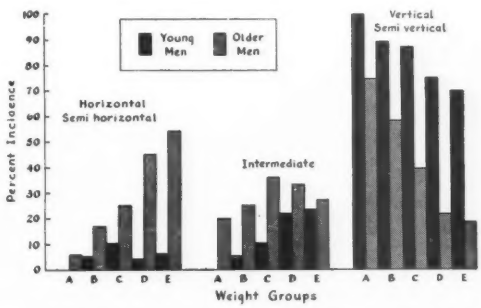

FIG. 4. Distribution of electrical heart position in young men and in older men, in five weight groups (A = underweight; E = overweight).

SUMMARY

1. Analysis according to age and relative body weight was made for 48 electrocardiographic items in the standard leads, unipolar limb leads, and CF_4 of 157 men from 18 to 25 years old and 233 men from 45 to 55 years of age, all of whom were found to be clinically normal in detailed examination.

2. The great majority of electrocardiographic items showed significant or highly significant differences between the two age groups and these differences were also shown when comparisons were restricted to men within ±5 per cent of standard weight for height and age. Significant age trends in V_R, V_L and V_F, were also found when identical heart positions were compared.

3. The mean values (and their standard deviations) in the young men were very similar to those for 1000 young aviators studied by Graybiel and his co-workers.

4. In general, the middle-aged men differed from the young men by exhibiting electrocardiographic tendencies in the direction of longer P-R intervals, lower voltages in all deflections, and left ventricular strain patterns. If current standards for young men are applied to the middle-aged men, "abnormal" values for the different items occurred in 5 to 10 or more per cent of the records.

5. Thirteen items showed statistically highly significant differences between lean and fat men. In some items there was a linear relationship with the relative body weight over the entire range. In a few items, for example the voltage in R_2 in young men, the relationship was curvilinear with a maximum or minimum in the men of intermediate relative body weight.

6. In general, the influence of relative body weight was more prominent in the older than in the younger men.

TABLE 10.—*Significant Differences of QRS Complex and T Wave between Underweight (<95 Per Cent Standard Weight) and Overweight (>105 Per Cent Standard Weight). Unipolar Limb Leads. Amplitudes in Standardized mm. (1 mm. = 0.1 mv.). Statistical Significance is Indicated by Asterisks as in Tables 8 and 9*

Heart Position and No. of Men	Lead	Item	Underweight		Overweight		Mean Δ
			Mean	s.d.	Mean	s.d.	
		Young Men					
V + SV (24 vs. 38)	V_L	R wave	0.57	0.37	0.91	0.84	0.34**
	V_L	S wave	−3.56	2.14	−2.88	1.53	0.68**
	V_L	T wave	−0.13	0.56	0.40	0.84	0.53***
	V_F	T wave	1.48	0.90	0.96	0.66	−0.52***
		QRS axis°	78.79	10.44	69.34	12.56	−9.45***
		Middle-aged Men					
V + SV (55 vs. 14)	V_L	R wave	0.67	0.51	1.13	0.75	0.56***
	V_L	T wave	0.21	0.55	0.55	0.48	0.34**
	V_F	S wave	−0.35	0.47	−0.01	0.05	0.34***
	V_F	T wave	1.39	0.82	0.80	0.63	−0.59***
		QRS axis°	70.40	13.82	62.78	18.30	−7.22**
		Middle-aged Men					
I (16 vs. 12)	V_L	Q wave	−0.36	0.48	−0.16	0.24	0.20*
	V_L	R wave	1.83	1.11	2.95	1.24	1.12***
	V_L	T wave	0.49	0.45	0.95	0.61	0.46***
	V_F	Q wave	−0.04	0.11	−0.12	0.27	−0.08***
	V_F	R wave	3.83	2.32	2.81	1.23	−1.02***
	V_F	S wave	−0.48	0.57	−0.10	0.27	0.38***
	V_F	T wave	1.38	0.84	0.77	0.39	0.61***
		QRS axis°	52.31	17.83	36.00	13.80	−16.31***
H + SH (8 vs. 18)	V_L	R wave	3.13	1.35	4.14	1.43	1.01*
	V_F	T wave	0.65	0.34	0.39	0.39	−0.26*

7. There was a pronounced tendency toward the horizontal electrical heart position with increasing body weight but many effects of relative obesity on the electrocardiogram are not explained on the basis of heart position.

8. In the unipolar leads numerous electrocardiographic items showed differences related to obesity, even when the same heart positions were compared.

9. There are similarities between the action of age and relative body weight in regard to the electrocardiogram but the two factors are not identical and must be considered separately.

10. An age and weight correction is necessary for a more precise definition of normal electrocardiographic standards.

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Myxoma of the Left Atrium

Diagnosis Made during Life with Operative and Postmortem Findings

By Henry P. Goldberg, M.D., Frank Glenn, M.D., Charles T. Dotter, M.D., and Israel Steinberg, M.D.

A case of intra-atrial myxoma manifested clinically by evidences of mitral stenosis and peripheral emboli is presented in detail. The diagnosis was made during life and confirmed by angiocardiography. The surgical procedure, attempted as a last resort, is described, as are the postmortem findings. This case points the way to possible surgical cure in similar lesions.

TO DATE, approximately 350 primary tumors of the heart have been reported. Prichard and Mahaim's reviews[1, 2] of the subject are notable. Approximately 126 of the reported primary cardiac tumors were myxomas, while 114 were sarcomas.[1, 3] Only five (all sarcomas) have been diagnosed correctly during life,[4–8] and in no case was angiocardiography employed. The surgical removal of an intracardiac tumor has not as yet been reported although the possibility of such a procedure has been speculated upon.[9] The following report is concerned with the clinical, operative and pathologic findings in a 3½ year old child with a myxoma of the left atrium. In this patient the lesion was suspected on the basis of clinical findings, established with reasonable certainty by angiocardiography, and proved at surgery and subsequent postmortem examination.

Case Report

The patient (N.Y.H. 591 973), a white male child 3 years of age, was first admitted to the New York Hospital on Feb. 6, 1951.* The child's past history was unremarkable except for measles at 2½ months and chicken pox at 6 months. The family history revealed rheumatic fever in the paternal grandmother and a paternal aunt. The patient had good health until March 17, 1950, when (at the age of 2 years and 3 months) he suddenly developed a right sided hemiparesis. The paralysis lasted for only 10 minutes, but weakness remained. He was admitted to another hospital where physical examination of the heart was unremarkable and laboratory studies did not clarify the cause of the hemiparesis. There was no change until the next month when he complained of the sudden onset of pain in his left foot. His mother noted "red spots" along the side of the foot. However the pain and discoloration subsided in a week and at no time were severe enough to lead to consultation with a physician. A second episode of brief paralysis of the right arm and leg occurred suddenly on Sept. 12, 1950. Residual weakness was more marked this time. A new finding was the presence of an apical systolic murmur. The third occurrence of paralysis of the right arm and leg was noted Oct. 22, 1950, 12 hours following a reported injury to his head. He was hospitalized again and had an uneventful course. Residual weakness was still marked. During the two months of this hospitalization several important cardiac abnormalities were noted. An apical systolic murmur was almost constantly present. An apical presystolic rumbling murmur was heard well at certain times and poorly or not at all at others. Fluoroscopy disclosed an enlarged left atrium and right ventricle. The four embolic episodes coupled with the appearance of signs of mitral stenosis in a 3 year old boy led to the consideration of a tumor of the left atrium as the primary condition.

Physical examination on transfer to the New York Hospital showed a well-developed 3 year old boy with weakness of the right arm, leg and face. There were increased resistance to passive extension, hyperactive deep tendon reflexes, positive Babinski and finger-stretch reflexes. The heart was not enlarged to percussion. There was an apical presystolic thrill. The first sound at the apex was accentuated and preceded by a rumbling crescendo murmur. The second pulmonic sound was not accentuated. The blood pressure was 110/70. There was no venous distention and the peripheral pulses were normal. The remainder of the examination was unremarkable. Extensive laboratory studies showed no significant abnormality. Fluoroscopy again showed a

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* Patient referred from the Roosevelt Hospital, New York City by Dr. Edmund Joyner.

l:rge left atrium and right ventricle but the left v-ntricle appeared normal in size. The pulmonary a teries were normal.

orifice (figs. 1 and 2). The left atrial appendage was uninvolved. These findings were interpreted as indicative of a tumor (probably a myxoma) within the

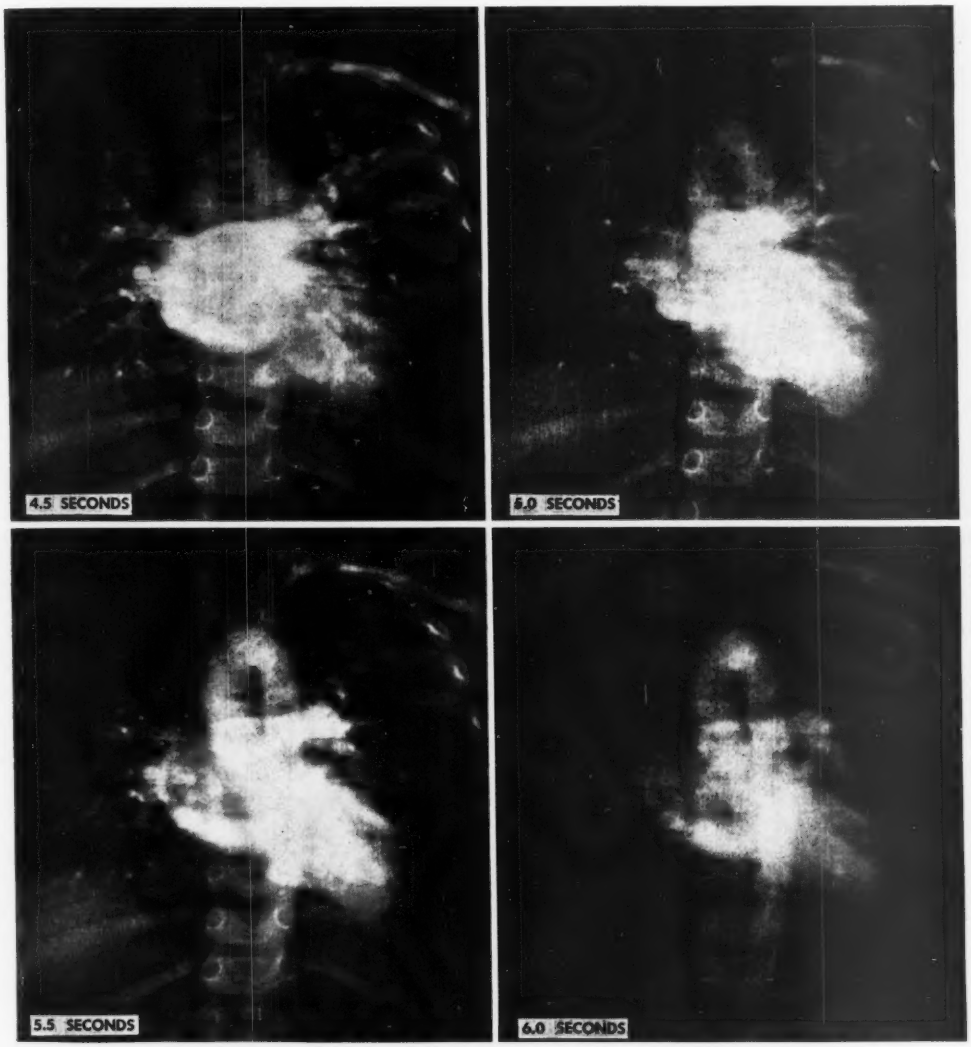

FIG. 1. *Angiocardiography.* Films selected from serial studies in frontal projection made following intravenous injection of 20 cc. of Urokon sodium (70 per cent). Between 4.5 and 6.0 seconds following the injection there was good opacification of the pulmonary veins, the left atrium and ventricle and the aorta. The left atrium was enlarged and was the site of a large irregular filling defect, present on all films.

The course in the hospital was unremarkable « cept for a brief generalized convulsion during » nepuncture. Angiocardiography demonstrated a rge, irregular, polypoid filling defect in the left trium anteriorly, immediately above the mitral left atrium. Surgical treatment was postponed in view of the great risk involved and in the hope that a satisfactory extracorporeal circulatory mechanism might become available soon.

The child was discharged from the hospital on

March 2, 1951. Shortly afterwards there was a transient episode of swelling and redness of the left second toe. A short course of x-ray therapy to the heart was given at another hospital during May of 1951 without any change in the cardiac findings. He was treated for bronchitis in April and pneumonia in May. During a visit to the New York Hospital Cardiac Clinic on July 25, 1951, he was noted to be in general good health. There was no change in the cardiac findings but fluoroscopy showed pulsatile dilatation of the pulmonary arteries.

On Sept. 12, 1951, the child developed edema of the face, arms and legs; the child was admitted to The New York Hospital two days later. He was acutely ill with obvious dyspnea and orthopnea. The cervical veins were distended. A firm and tender liver edge was palpated 8 cm. below the costal margin. The lungs were clear; the respiratory rate was 36. The heart rate was 132 and the blood pressure 108/70. The heart was enlarged to the left. The other cardiac signs were unchanged. Edema was not noted. Venous pressure was 440 mm. saline and the fluorescein circulation time from arm to lips was 16 seconds. Electrocardiography showed right axis deviation, a notched P_1 and variable widening of P_2. Digitalization and oxygen therapy led to moderate improvement but the liver edge remained 5 cm. below the costal margin and venous pressure only fell to 255 mm. saline. Digitalis dosage was extended to early toxicity and Mercuhydrin was given every day for a week. Improvement did not result however and attacks of cyanosis and dyspnea necessitated the use of oxygen therapy. With the realization that surgery offered the patient his only chance for survival this was undertaken on Oct. 11, 1951, 19 months after the onset of symptoms.

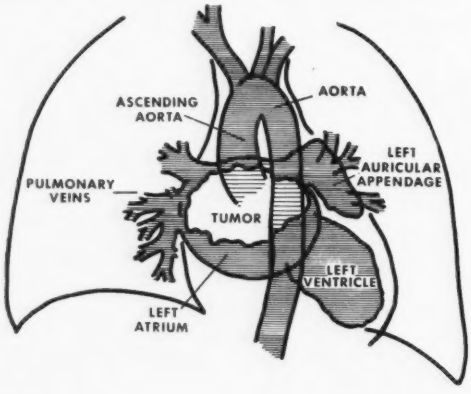

FIG. 2. Tracing of 6.0 second film (fig. 1) showing filling defect in the enlarged left atrium. Lateral studies indicated that the mass was situated in the anterior portion of the left atrial cavity, just above the site of the mitral valve orifice.

The patient, who had been receiving oxygen therapy, was taken to the operating room in his bed and anesthetized by the addition of cyclopropane to the oxygen circuit. An intratracheal tube was inserted and a slow infusion of blood and 5 per cent glucose in distilled water was started by means of intravenous plastic cannulae placed through cut-downs in each leg. The patient was positioned on his back with the left side slightly elevated and the skin was prepared and draped so as to expose the left chest. At this point there had occurred no perceptible change in the patient's condition; the color of skin and mucous membranes was normal, the pulse was 160 and the blood pressure was 90/50.

A curving incision, started at the level of the left second rib in the midsternal line, was carried below the breast area into the left axilla. The pectoral muscles were reflected from the chest wall and the third rib resected subperiostially from the costosternal junction to the midaxillary line. Upon entry into the left pleural space, the lung which was heavy and edematous, did not collapse. There was approximately 200 cc. of straw colored fluid in the left chest. The heart appeared moderately enlarged and the pericardium was full and tense, especially at the upper portion over the left atrium. Two cubic centimeters of 1 per cent novacaine were introduced into the pericardial sac and within two minutes the heart rate began to slow. Over the next two minutes it came to a standstill. Manual cardiac massage was instituted and continued for 20 minutes without reestablishment of cardiac action. It was then decided to attempt removal of the tumor since it was believed to be occluding the blood flow through the left heart. An incision was made in the pericardium, parallel and medial to the phrenic nerve, over the pulmonary artery and down to the midportion of the left ventricle. The left atrium was found to be prominent and a firm resistance on palpitation suggested that it contained a tumor.

When the atrial appendage was opened, a mass consisting of many small, glistening, semitranslucent, globular bodies bulged up into it from the atrium (fig. 3). Although poor cardiac contractions occurred at this time, no blood escaped into the atrial appendage from around the tumor. By using a pituitary rongeur, projections of the tumor were readily removed. As each pull with the instrument brought away 1 or 2 cc. of tumor, more of the same material appeared at the orifice of the appendage. After 10 or 12 cc. had been removed with the rongeur, a pituitary spoon was introduced into the atrium, and further large globs or segments of tumor were freed from its base and delivered through the appendage. The small finger of the left hand was then introduced into the left atrium through the appendage. The base or stalk of the tumor could be palpated and seemed to be about 3 cm. in diameter,

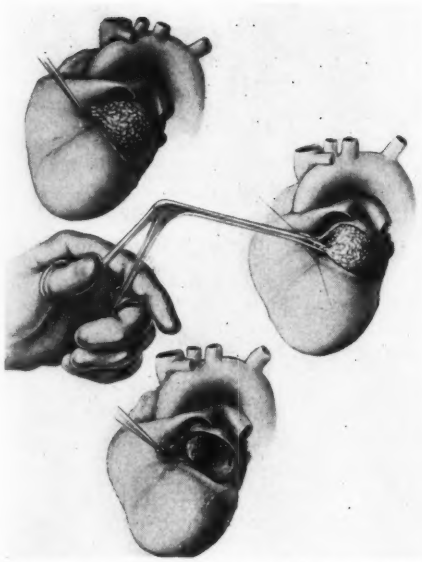

FIG. 3. *Surgical Procedure* (artist's reconstruction). When the atrial appendage was opened, the polypoid tumor mass bulged out (above). Small portions of the projecting mass were removed with a pituitary rongeur (middle), reducing the volume of the tumor and leaving the left atrium relatively free for the passage of blood (below).

arising from the interatrial septum. It was rather soft and about 1 cm. in elevation. Following removal of the majority of the mass, blood filled the atrium, the walls of which were readily compressible. The mitral valve was normal to palpation. Examination of the material removed revealed numerous small fragments of soft, gelatinous, somewhat lobulated, translucent, yellow tissue, the total volume of which was approximately 30 cc.

Removal of the tumor required about six minutes, following which a pursestring suture, previously placed at the base of the atrial appendage, was drawn up and secured and the distal portion of the appendage closed with interrupted sutures of fine silk. Cardiac massage was resumed. The myocardium was bathed in a 1 per cent solution of procaine, followed by an injection of 1 cc. of calcium chloride into the wall of the left ventricle and 1 cc. of adrenaline into the chamber of the left ventricle. Good cardiac action reappeared for the first time since the primary cardiac arrest 40 minutes before. The blood pressure reached a maximum of 90/50. After a period of observation, the pericardium was partially reapproximated and the chest closed. Twenty minutes after completion of the operation, and 2 hours and 40 minutes after the first cardiac arrest, heart contractions again became irregular and irreversible standstill occurred within five minutes.

Postmortem examination (N. Y. H. Autopsy 14,349) revealed that the tumor mass, portions of which remained attached to a broad flat pedicle,

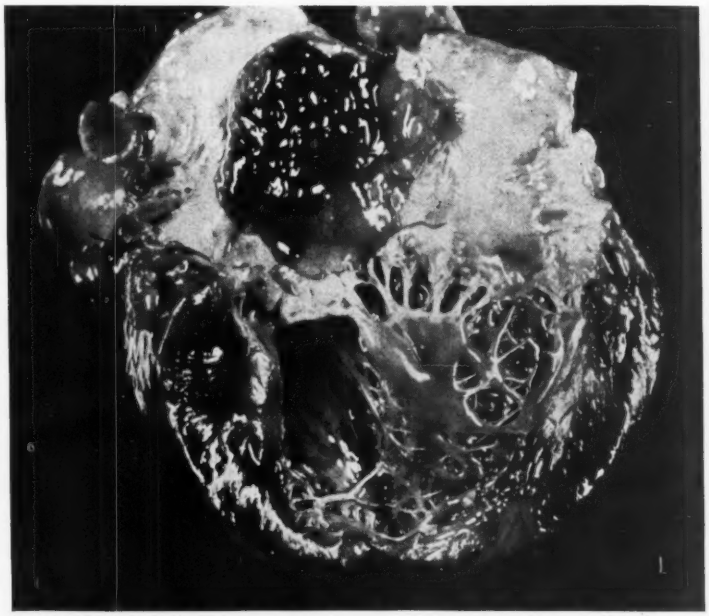

FIG. 4. *Gross Pathology.* The tumor arises from the anterior portion of the interatrial septum just above the mitral valve orifice. The chordae tendineae of the mitral valve are shortened and thickened.

took origin from the interatrial septum at a point anterior to the foramen ovale (fig. 4). As had been noted at operation, the tumor had a multilobular character and was moderately gelatinous in consistency. Microscopic examination (fig. 5) disclosed that the tumor was covered by endocardium and consisted of an evenly stained acidophilic myxomatous stroma. The cells, often multinucleated, were widely spaced and had stellate cytoplasm. There was no evidence of malignancy.

The histologic diagnosis was myxoma. The right ventricle was moderately hypertrophied, its wall measuring 6 mm. in thickness. The edges of the

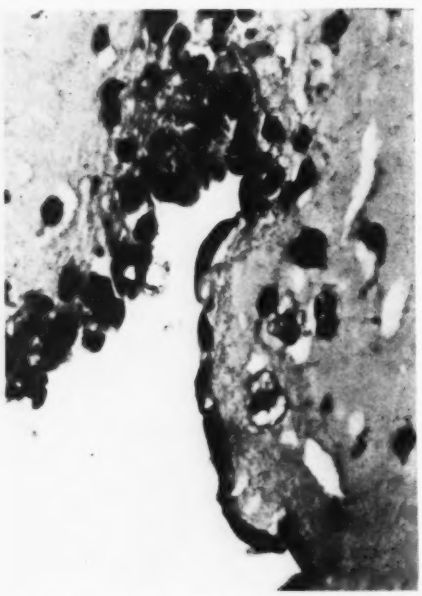

FIG. 5. *Histology* (×700) A layer of endothelial cells covered the tumor which was composed of a myxomatous stroma containing sparsely scattered nuclei. There was no cytologic evidence of malignancy. The diagnosis was myxoma arising from the interatrial septum.

mitral valve and the chordae tendineae were thickened, possibly as a result of direct trauma caused by the tumor itself. Although it is conceivable that this change in the valve and chordae tendineae may have been a result of rheumatic fever, careful study of many sections of the heart revealed no Aschoff bodies. There was evidence of previous embolic infarction in the left cerebral hemisphere and the kidneys.

DISCUSSION

Diagnostic Considerations

Although the antemortem diagnosis of primary tumor of the heart has been made five times previously, the present case is believed to represent the first recorded instance where the diagnosis of an intracardiac myxoma was made during life. The lesion was suspected for the following reasons:

Changing auscultatory signs suggested the presence of obstruction of the mitral valve not present at birth and therefore presumably not of congenital origin. The development of rheumatic mitral stenosis prior to the age of 3 in a child who had shown no evidence of rheumatic fever was considered to be unlikely. Repeated embolic episodes are frequently associated with intracardiac tumor masses, especially myxomas. The most likely diagnosis was thought to be that of an intracardiac tumor causing obstruction to the mitral orifice although it was considered possible that valvular stenosis coupled with intra-atrial thrombus formation could have caused the clinical picture. It is of interest in this connection that auricular fibrillation was never noted.

Angiocardiography in frontal and lateral projections established beyond doubt that a polypoid mass, approximately 5 by 3 by 3 cm. in size was located in the anterior portion of an enlarged left atrium, apparently attached to the interatrial septum and in a position capable of occluding the mitral orifice. No pedicle could be detected. This angiocardiographic examination, performed eight months prior to surgery, is believed to constitute the first visualization of a proved intracardiac tumor in the living patient.* Mahaim[2] correctly suggested that angiocardiography might afford a means for the identification of such lesions during life. It is apparent that many of the reported cases of intracardiac tumor would have been strikingly demonstrated had angiocardiography been available or employed.

Surgical Considerations

At the time operation was undertaken on the patient reported here the tumor virtually

* A 52 year old female with similar angiocardiographic findings is being followed currently in the clinics of the New York Hospital. Cardiac catheterization indicated the presence of physiologic mitral stenosis of a mild degree probably due to mechanical interference with blood flow through the mitral valve caused by the large tumor mass.

filled the left atrium, markedly impeding the flow of blood. Progressive deterioration of the patient's status had occurred during the period prior to surgery and thorough digitalization did not reverse decompensation. Although the induction of anesthesia and the prone position were well tolerated, opening the chest and introduction of 2 cc. of procaine into the tense pericardial cavity was followed by cardiac arrest. It seems logical to assume that a change in intra-atrial pressure or a shift in the position of the tumor mass cut off blood flow and resulted in catastrophe.

In retrospect, it is felt that in the face of cardiac arrest it might have been more logical to proceed immediately with removal of the tumor, postponing cardiac resuscitation until this had been accomplished. Had this been done, the period of anoxia might have been six or seven instead of 40 minutes. Such tumors, if they are to be removed successfully, should be operated upon before they have grown so large as to fill the left atrium, impede the blood flow and give rise to cardiac failure. Since intracardiac myxomas are usually benign lesions, surgery would appear to be indicated in certain instances, and, it is predicted, will eventually prove to be a curative measure. The development of apparatus for maintenance of the extracorporeal circulation would be of obvious value.

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Pulmonary Embolism

By LOUIS WOLFF, M.D.

THE HIGH RATE of morbidity and mortality for which pulmonary embolism is responsible, is clearly revealed by a study of the incidence of thromboembolism[1] and emphasizes its great importance. Venous thrombosis in the deep veins of the legs, the most common cause of pulmonary embolism, has been demonstrated at autopsy in 50 per cent of all patients who had been confined to bed; the number of medical and surgical patients were equal.[2] Pulmonary embolism was found in 10 per cent of all autopsies, and was considered to be the cause of death in 3 per cent of all autopsied patients.[3] The clinical incidence of venous thrombosis and pulmonary embolism, however, is considerably less than the above figures would indicate, namely 0.5 per cent to 1.6 per cent of postoperative patients, 1 per cent of general hospital admissions, and 1.2 per cent of postpartum patients.[1, 4, 5]

It is essential, in discussing pulmonary embolism, to have a clear understanding of the meaning of the various terms commonly employed in dealing with this subject. Pulmonary embolism refers to the migration of gaseous or particulate matter from any portion of the cardiovascular system peripheral to the pulmonary artery, and its lodgement in the pulmonary arterial tree. In this paper the discussion will be limited to the migration and lodgement of aseptic blood clots (bland emboli). Thus, the emboli may come from the valves or chambers of the right heart, or the vast venous channels leading to the right heart. Pulmonary thrombosis is the erection in situ of a thrombus in the pulmonary vascular tree, and although the end result may be the same as when pulmonary embolism occurs, it represents a different entity, and is not included in our discussion.

Local circulatory disturbances, as well as abnormal reflexes, consequent to pulmonary embolism, may result in atelectasis, edema, hemorrhage, inflammation, and necrosis of the lung parenchyma and pleura. Resolution and complete restitution to normal may take place if only the first four processes occur (preinfarction), but fibrosis will be the end result if there is destruction of pulmonary parenchyma (infarction).

Another possible consequence of pulmonary embolism is the acute cor pulmonale. This term is applied to a group of clinical, roentgenologic, and electrocardiographic findings which embrace the following: a prominent pulsation in the second and third intercostal spaces to the left of the sternum; dilatation and pulsation of the jugular veins; cyanosis; accentuation of the pulmonic second sound; at the pulmonic valve area, a loud systolic murmur, sounds resembling a pericardial friction rub, a gallop rhythm, and a palpable shock corresponding to closure of the pulmonic valve; and dilatation and overactivity of the pulmonary artery and conus. The characteristic electrocardiographic changes of acute cor pulmonale will be discussed below. This entire syndrome may be obscured by the rapid development of peripheral vascular collapse, or right heart failure may supervene.

Pulmonary embolism, then, may or may not be followed by pulmonary infarction (or preinfarction), and/or acute cor pulmonale. Many other manifestations consequent to pulmonary embolism commonly occur, and these will be discussed below. Pulmonary infarction and

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acute cor pulmonale occur in the absence of pulmonary embolism, and therefore, are not pathognomonic of the latter. Nevertheless, the diagnosis of pulmonary embolism is made largely on the basis of symptoms, signs, and laboratory findings associated with pulmonary infarction and acute cor pulmonale. The acute cor pulmonale, in addition to providing valuable diagnostic signs, indicates grave functional abnormalities, while pulmonary infarction, except when extensive, is of little importance save for the diagnostic signs which are furnished by it.

Etiology

A free floating or detachable clot in the vascular system distal to the pulmonary artery is the one condition essential for pulmonary embolism. Theoretically, then, the source of embolism may be the chambers and valves of the right side of the heart or any part of the extensive venous channels draining into it. Actually, the great majority of emboli come from the deep veins of the legs, a few come from the pelvic plexus of veins, or from the right side of the heart, and the remainder, which are extremely rare, originate in the large veins of the upper extremities.

The mechanism responsible for the intravascular formation of blood clots is poorly understood. The preponderance of thromboembolism in bed-ridden and postoperative patients, and under conditions in which injury to the vessel wall may be sustained (mechanical trauma, infection) emphasizes the importance of two of the factors which are related to the clotting process: slowing of the blood stream, and injury to the vessel wall. The occurrence of thromboembolism in patients with polycythemia or other hematologic abnormalities, after the administration of certain drugs, and following rapid diuresis, has led to the notion that changes in blood composition play a part in venous thrombosis. In spite of extensive investigation of this subject, little is actually known concerning it.[1]

The two outstanding facts in relation to the etiology of pulmonary embolism are its preponderance in bed-ridden* patients and its negligible incidence, apart from obstetric cases, in patients under 30 years of age. Contrary to previously held views, most cases occur in nonsurgical patients with a notably high incidence in those with heart disease. Even in those with heart disease the heart itself is not often the source of the emboli.

Pulmonary embolism is uncommon in apparently healthy, ambulatory individuals. In such individuals it results from "idiopathic thrombophlebitis," a condition which is distinguished by the following features: it occurs almost without exception in males, in contradistinction to the slight predominance of males in the entire group of thromboembolism; two-thirds of the patients have recurrent episodes of phlebitis; about one-third of the patients develop pulmonary embolism; and one-tenth of the patients eventually display evidence of malignant tumors, polycythemia, or thromboangiitis obliterans.[6]

Pathologic Physiology

Many of the phenomena which are observed in pulmonary embolism can be attributed directly to obstruction of blood flow in the pulmonary arterial system. The sudden vascular obstruction is immediately followed by local disturbances in the pulmonary circulation, a sharp rise in right ventricular pressure, and a drop in left ventricular pressure; the latter may result in coronary failure. Pulmonary obstruction, therefore, plays a direct part in the development of pulmonary infarction, the syndrome of acute cor pulmonale, peripheral vascular collapse, and certain of the cardiac disorders which are occasionally associated with pulmonary embolism. However, clinicopathologic correlation between the number of clinical episodes and the number of emboli which can be recognized at autopsy is very imperfect, clearly indicating that many emboli are "silent," and suggesting that some of the clinical manifestations are consequent to reflexes originating in inflamed veins or in arteries lodging emboli. These reflexes involve the pulmonary vasculature, the bronchi, the diaphragm, the coronary arteries, the neurogenic mechanism of the heart, and the peripheral vascular system. Anoxia, which is

* Bed-ridden does not necessarily imply prolonged confinement in bed. Venous thrombosis may occur in patients with a feeble circulation after 24 hours of complete, or almost complete immobility.

frequently a striking feature of pulmonary embolism, can be explained on the basis of some of these reflexes as well as on such pulmonary abnormalities as atelectasis, infarction, and congestion.

The lodgment of a clot in a pulmonary artery, therefore, produces local disturbances in pulmonary circulation, pulmonary hypertension, a lowering of systemic pressure, abnormal reflexes, and anoxia, and these elements provide the basis for all the phenomena observed in pulmonary embolism. The particular functional and structural alterations which follow pulmonary embolism will depend on the proportionate role of these elements, which are closely interrelated, and upon the following factors: the caliber of the vessels occluded, the extent of propagation of the emboli within these vessels, and the pre-embolic state of the heart, lungs, and circulation.

The Clinical Picture

The numerous clinical manifestations observed in pulmonary embolism develop as a result of the complex interplay of the various elements mentioned in the preceding paragraph. Pain is related to local disturbances in pulmonary circulation, to pleural involvement, and to impairment of coronary circulation. Dyspnea has a manifold origin, stemming from bronchospasm or vasospasm, disturbances in pulmonary circulation, immobility or diminished respiratory excursion of the diaphragm, atelectasis and/or pulmonary infarction, anoxia, and impairment of cardiac function. Anoxia is manifested clinically by cyanosis. Hyperbilirubinemia may occur when anoxia, pulmonary infarction, and hepatic congestion coexist. Pulmonary hypertension, anoxia, and coronary failure, are responsible for the abnormal cardiac signs, including all the manifestations of acute cor pulmonale and congestive heart failure. Some of the clinical phenomena which have been attributed, at least in part, to abnormal reflexes are dyspnea, asthmatic breathing, pulmonary edema, syncope, atelectasis, and peripheral vascular collapse. Pulmonary preinfarction and infarction are closely related to the circulatory disturbances resulting from pulmonary obstruction.

Dyspnea, chest pain, and cough are the most frequent symptoms, and fever, tachycardia, abnormal pulmonary signs, and peripheral vascular collapse are the most common physical findings. Cyanosis, hemoptysis, syncope, and the various manifestations of acute cor pulmonale are less commonly observed. Jaundice, coma, sudden weakness, convulsions, nausea, vomiting and hiccough are occasional findings.

These manifestations occur singly, or in various combinations. A characteristic feature is their intermittent appearance so that the clinical course may consist of a series of episodes with intervening silent or relatively silent periods. The manifestations may be the same in different episodes, or there may be no resemblance between one episode and another. Contrary to the observations of others,[7, 8] we have been impressed by the frequency and multiplicity of symptoms and signs, and if these are properly appraised, sudden unexpected death from pulmonary embolism should be a much rarer experience than it is. For example, a brief syncopal attack, or a short paroxysm of auricular fibrillation may be the sole warning, hours or days before sudden death. Since early diagnosis of thromboembolism is essential for the institution of therapeutic measures to avoid fatalities, the prompt recognition and proper interpretation of such developments is important.

Chest pain is the most common single manifestation of pulmonary embolism. It occurs in about 75 per cent of the cases. Pleuritic pain was noted in 54 and anginal pain in 26, of 108 patients with pulmonary embolism recently studied.[9] Although pleuritic pain was a complaint in one-half of the patients, a pleural friction rub was observed in only 10 per cent of the group, and pleural effusion was but seldom recognized. However, small amounts of fluid may accumulate in one or both pleural cavities, and rarely, recurring pleural effusions of large size may dominate the clinical picture. The fluid is often sanguineous, but otherwise does not display any characteristic features.

The anginal type of pain may closely

simulate either angina pectoris or acute myocardial infarction, although certain differences, referred to later, can usually be discerned. Its occurrence does not depend on the presence of pre-existing heart disease, and there is no predilection for males or the older age groups as is true in coronary heart disease.

Dyspnea is noted by almost half of the patients, its incidence being exceeded only by pain. It may be mild or severe, and wheezing respiration or frank pulmonary edema may occur; the latter is not uncommon. A characteristic feature of pulmonary embolism is severe dyspnea without obvious evidence of pulmonary or heart disease.

Cough is almost as common as dyspnea, occurring in over one-third of the patients, and hemoptysis is evident in one-fourth of the cases.

Abnormal signs, as mentioned above, are extremely common. Fever occurs in about two-thirds and tachycardia in over one-half of all patients with pulmonary embolism. There is no characteristic febrile curve, except that sharp spikes in temperature are common, and fever is usually present at the time clinical manifestations are first noted. Sustained fever up to 103 F. or 104 F. for days or a week or more may be observed, with gradual fall to normal. Occasionally fever is the only recognizable manifestation of pulmonary embolism, the patient presenting the problem of fever of unknown origin. A remarkable feature, and one in striking contrast to the great incidence of fever, is the rarity of shaking chill in the absence of complicating sepsis.

Pulmonary signs are observed in well over half of the patients. They are due to atelectasis, preinfarction, infarction and pleural effusion, and embrace localized areas of dullness, crepitant rales and bronchial breathing. These signs may be found anywhere in solitary or multiple areas, but are most common at the right base. They may disappear completely in hours or days, or may persist for a week or longer.

Sudden vascular collapse is one of the characteristic features of pulmonary embolism. It may be the first indication of trouble, antedating by hours or days other manifestations of thromboembolism. There may be a single attack of transient or sustained vascular collapse, or repeated episodes may occur. The transient attacks resemble ordinary syncope. In some cases vascular collapse is associated with, or may precede or follow pulmonary edema, chest pain, the advent of pulmonary signs, or paroxysmal rapid heart action. Occasionally, a pronounced, temporary rise in blood pressure is associated with anginal pain.

Some of the most characteristic, though less common physical signs involve the heart and pulmonary artery, and were referred to previously as the acute cor pulmonale. A prominent pulsation, due to dilatation and overactivity of the pulmonary artery and conus, may be visible or palpable in the second and third intercostal spaces to the left of the sternum, and dilatation and pulsation of the jugular veins, and cyanosis, may be noted. Auscultation at the pulmonic valve area may disclose marked accentuation of the second heart sound, a loud systolic murmur, sounds resembling a pericardial friction rub, and a pronounced protodiastolic gallop rhythm. A shock corresponding to closure of the pulmonic valve may be palpable. These signs appear suddenly, but may be transient if peripheral vascular collapse or right heart failure supervene.[10]

Paroxysmal auricular fibrillation is an occasional complication of pulmonary embolism, and, like vascular collapse, may be the first indication of trouble, antedating by hours or days other manifestations of thromboembolism. Paroxysmal auricular tachycardia and paroxysmal auricular flutter occur less frequently. High grade A-V block and paroxysmal ventricular tachycardia have not been observed by the writer in uncomplicated instances of pulmonary embolism.

Thus, the "typical" clinical picture of pulmonary embolism will be characterized by chest pain, dyspnea, cough, fever, pulmonary signs, and tachycardia. Syncope, hemoptysis, and the various manifestations of acute cor pulmonale will be observed in some of the cases. The clinical course will be distinguished by the episodic appearance of these manifestations, separated by silent intervals. However,

the variety and changing combinations of the many symptoms and signs frequently impart a remarkably variegated, and at times, bizarre character to the clinical picture. The clinical picture in many cases, therefore, does not conform to the text book description of pulmonary embolism, but simulates many other disorders. The more common of these are angina pectoris, acute myocardial infarction, simple pleurisy, pleurisy with effusion, tuberculosis, pneumonia, acute heart failure, asthma, tumor, diseases of the central nervous system, and psychoneurosis.

Laboratory Observations

The electrocardiogram frequently displays features which are helpful in the diagnosis of pulmonary embolism, and should be obtained whenever this condition is suspected.[11] If tracings are taken immediately, and repeated daily, or after each clinical episode, until the diagnosis is definitely established or excluded, transient electrocardiographic changes will be observed in about three-fourths of the cases. The pattern of acute cor pulmonale is the most characteristic of these, and is noted in one half of the cases. Its main features are large S deflections in lead I, prominent Q and inverted T waves in lead III, and in some of the cases, inverted T waves in the right sided precordial leads. The sudden appearance and rapid evolution of these changes, and the rather rapid return to normal, distinguishes these tracings, and helps to differentiate them from examples of posterior myocardial infarction. In addition, the QRS complex in lead aV_F is normal, except in rare instances, whereas in posterior myocardial infarction an abnormal Q wave is frequently noted. Another electrocardiographic change of diagnostic importance is the sudden appearance of transient, incomplete right bundle branch block. Finally, in many cases the only abnormality noted is transient inversion of the T waves in the right sided precordial leads. Although of considerable diagnostic significance, these abnormalities are not pathognomonic of pulmonary embolism and are observed in other conditions.

The usefulness of the electrocardiogram as a diagnostic aid is limited by the fact that changes characteristic or suggestive of pulmonary embolism do not always occur. This deficiency is especially common in the presence of heart disease which alters the electrocardiogram, as, for example, acute myocardial infarction. When pulmonary embolism complicates acute myocardial infarction, or vice versa, electrocardiograms will display the features characteristic of acute myocardial infarction, rather than those which can be recognized as indicating pulmonary embolism.

Roentgenologic study may disclose highly significant signs, the most common being areas of plate-like atelectasis, and truncated shadows corresponding to areas of preinfarction or infarction. These are better detected by fluoroscopy than by ordinary films. Fluoroscopy also allows the demonstration of dilatation and overactivity of the pulmonary artery and conus, and abnormal behavior of the diaphragm, characteristic features of pulmonary embolism which might otherwise remain undisclosed. The diaphragm on the involved side is often high, and may exhibit diminished or absent respiratory excursions. Occasionally one may observe an occluded pulmonary artery and the avascular pulmonary shadow representing the bloodless lung it once irrigated. The avascularity imparts an appearance of increased translucency to the portion of lung parenchyma affected, so that the picture of localized pulmonary emphysema is simulated. During the acute stage the pulmonary artery lodging an embolus is surrounded by a hazy irregular shadow due to edema of the adjacent tissues.

As the acute inflammatory reaction subsides, the shadow of the occluded pulmonary artery becomes more clearly distinct, and eventually is abruptly demarcated from the surrounding structures, giving the appearance of an amputated hilar shadow.

Leukocytosis occurs in about 70 per cent of the patients. The elevation in white cell count is usually only moderate, with a slight shift to the left, even when extensive pulmonary infarction is present. Leukocytosis may persist for days at a time, or may appear and disappear without apparent reason. Leukocytosis may be noted when other signs of thromboembolism are absent.

The sedimentation rate is increased, at times markedly so.

Hyperbilirubinemia occurs in about half of the cases.

Diagnosis

The diagnosis of pulmonary embolism rests on two groups of facts, those pertaining to etiology, and those embracing the numerous symptoms, signs and laboratory findings which comprise the clinical picture described in a preceding section. In many instances the clinical and laboratory phenomena are so characteristic, that there is no difficulty in making the diagnosis. The diagnosis should be clearly evident when an elderly, bedridden patient suddenly develops dyspnea, cough, and pleuritic pain, and examination reveals a sharp rise in temperature, pulmonary consolidation, and leukocytosis. The signs may be less characteristic, perhaps a small area of dullness and crepitant rales, or highly suggestive, such as hemoptysis and a pleuritic friction rub. Or the diagnosis may appear evident because the various features which distinguish acute cor pulmonale are observed, or pulmonary infarcts or an occluded pulmonary artery and related phenomena are demonstrated roentgenographically, or the changing electrocardiographic patterns indicative of pulmonary embolism are noted. These phenomena are so characteristic of pulmonary embolism that they may be considered diagnostic. In some cases the diagnosis is strongly suggested, not so much by the special character of the clinical features, as by the clinical course, i.e., the explosive and episodic appearance of various manifestations separated by silent intervals.

On the other hand, the diagnosis may be missed when bizarre combinations of symptoms and signs occur, or when there is only an isolated symptom or sign, as is so often the case, at least during part of the clinical course. Furthermore, the clinical phenomena which occur may be the uncommon and less characteristic ones; these lack diagnostic importance unless their significance is enhanced by pertinent etiologic factors. For example, paroxysms of auricular fibrillation, or brief syncopal attacks, occur under such diverse conditions that consideration of pulmonary embolism as a possible cause will be necessary only when they occur in individuals who are likely candidates for thromboembolism, that is, in those past middle age who have been confined to bed, and those who have sustained recent leg trauma or infection. In such cases, the presence of deep venous thrombosis in the lower extremities, the most common immediate cause of pulmonary embolism, may be the most useful clue to embolism as the explanation of these phenomena. The necessity of careful and repeated examination of the limbs, when attempting to establish a diagnosis of pulmonary embolism, is evident. Tenderness in the plantar veins of the foot, or in the calf muscles is an early sign. Tenderness along the course of the great veins on the inner aspect of the thighs, swollen and tender inguinal lymph nodes, and pitting edema, are later developments. However, thrombophlebitis in the lower extremities may exist without producing any signs or symptoms, and venography, properly executed, may reveal its presence. If no evidence of phlebitis is found, some other site of origin of the embolus may be looked for. It cannot be emphasized too strongly that embolism should never be excluded merely because phlebitis cannot be demonstrated. In fact, the diagnosis of pulmonary embolism must frequently be made without definite proof of the existence of phlebitis.

The diagnostic problems in this field are considerable, and errors both of omission and commission are not infrequent; failure to make the diagnosis is the more serious of these. A high index of suspicion is the first necessary step for correct diagnosis, since remarkably little may be apparent to suggest the diagnosis of pulmonary embolism. Once the condition is thought of, however, thorough elicitation of symptoms and signs, careful roentgenologic and electrocardiographic study, and examination of the extremities for evidences of phlebitis, may reveal signs of diagnostic significance which otherwise might have escaped recognition. Pulmonary embolism must be suspected in every elderly, bedridden patient in whom the clinical course is unfavorable, or who develops chest pain of anginal or pleuritic type, or acute dyspnea. It is necessary to

consider embolism whenever a patient with heart failure does not respond to treatment in the expected manner, or a diagnosis of angina pectoris, acute myocardial infarction, dissecting aneurysm, pneumonia, or "infectious" pleurisy is entertained but not established. Furthermore, embolism must be considered whenever patients who are likely candidates for thromboembolism display any of the following phenomena: unexplained vascular collapse, unexplained syncope, paroxysmal auricular fibrillation, hemoptysis, unexplained fever, pulmonary edema especially when not readily explained by the underlying disease, cyanosis, and jaundice. Deep cyanosis, acute dyspnea, and pulmonary edema, in the absence of obvious pulmonary or heart disease, are strongly suggestive of pulmonary embolism.

The greatest difficulty in diagnosis is encountered in patients who have anginal pain, thus raising the question of angina pectoris or acute myocardial infarction. In spite of the similarity in many of the manifestations of pulmonary embolism and coronary disease, differences exist which make possible the differential diagnosis. When pulmonary embolism is the cause of anginal pain there may be distinct pleuritic pain in addition, or the anginal pain may be intensified by inspiration, a feature which is not observed in angina pectoris or at the onset of acute myocardial infarction. Syncope is common in pulmonary embolism, and particularly distinguishing is its occurrence prior to the onset of pain. On the other hand, syncope is uncommon in coronary disease, especially prior to the occurrence of pain. Paroxysmal auricular fibrillation occurs in both conditions, but when it precedes pain it is more likely to be due to pulmonary embolism than to acute myocardial infarction. Tachycardia and a pronounced fall in blood pressure are the rule early in the course of pulmonary embolism whereas at the onset of acute coronary disease, bradycardia is common, and, as a rule, blood pressure changes are not striking; indeed, not infrequently the blood pressure rises simultaneously with the onset of pain in coronary disease. Fever, leukocytosis, and an increased sedimentation rate are commonly present at the time clinical manifestations are first noted in pulmonary embolism, but are rarely observed in the first 24 hours in acute myocardial infarction. Paroxysmal ventricular tachycardia and high grade A-V heart block are fairly common complications of acute myocardial infarction, but do not occur in pulmonary embolism. Evidence of pericarditis excludes the diagnosis of pulmonary embolism, and pleurisy rules out uncomplicated acute myocardial infarction.[12] Finally, electrocardiographic and x-ray studies expertly interpreted are helpful.

Prognosis

Pulmonary embolism is one of the important causes of morbidity and mortality in postoperative patients, and in bedridden nonsurgical patients past middle age. While recovery frequently occurs, the threat of sudden death is ever present, and the mortality rate rises sharply with each embolism when recurrent episodes occur. It is a common cause of sudden and unexpected death, although the element of surprise, judging from our experience, is due to failure to appreciate some of the early warning signs. Grave disturbances involving the heart, lungs and circulation occur, but if a fatal issue is avoided, complete recovery may be anticipated almost without exception. In the rare instances in which repeated embolization occurs over a period of years, cardiac enlargement and finally, chronic congestive failure, ensue. The features are those of chronic cor pulmonale.

Treatment

Since pulmonary embolism is most commonly the consequence of deep venous thrombosis in the lower extremities, its incidence could be materially reduced by the prevention of thrombophlebitis. The numerous methods and procedures which are practiced with this end in view testify to the importance which is widely attributed to this etiologic factor, and to the difficulty in preventing venous thrombosis. Early ambulation of surgical and other patients, active and passive movements of the legs, massage, wiggling of the toes, leg binders of one sort or another, and avoidance of pressure on the soft parts of the limbs, are some of the measures employed.[13] Prophylactic vein

ligation prior to surgery in elderly patients has not been demonstrated to have appreciably reduced the incidence of pulmonary embolism, but is believed by some observers to be a worthwhile precaution.[14] More recently anticoagulants have been administered prophylactically, mostly to patients with acute myocardial infarction and congestive heart failure, with impressive results.

The treatment of pulmonary embolism is still the subject of some controversy. It cannot be denied that many patients recover without having had specific therapy, even after multiple embolic episodes, or that death occasionally occurs in some cases despite early diagnosis and prompt and vigorous treatment. Nevertheless, the mortality rate can be reduced by treatment, although no single known form of therapy can assure recovery in every case. Treatment by oxygen inhalation, morphine, atropine, papaverine, digitalis, antibiotics, and plasma or blood though purely supportive and symptomatic, is of considerable importance. The prompt institution of measures to promote the comfort of the patient and support the circulation may be an urgent necessity, and takes precedence over other therapy. Pain, dyspnea, vascular collapse, cyanosis, and paroxysmal rapid heart action are the most important indications for the various therapeutic measures mentioned above. Oxygen is useful when there is cyanosis, dyspnea, or vascular collapse, and morphine is of value for its sedative and analgesic effect, and for the control of dyspnea. The combined use of papaverine and atropine may have a strikingly beneficial effect on dyspnea. Plasma or blood appears to be helpful in the presence of vascular collapse. Paroxysmal auricular fibrillation and paroxysmal auricular tachycardia should be treated with digitalis, which otherwise is rarely of any use in pulmonary embolism. Antibiotics are frequently given to prevent pulmonary infection, but their value is dubious unless there is clear cut evidence of infection.

Surgical interruption of the large venous channels of the lower extremities or of the inferior vena cava, or anticoagulant therapy is employed as soon as the diagnosis of embolism or phlebitis is made, in order to forestall the discharge of a first or a subsequent embolus. There is some question as to the relative merits of heparin and dicumarol or similar substances. In view of the necessity of injecting heparin intravenously it would seem desirable to use it in addition to dicumarol only to initiate therapy when an immediate anticoagulant effect is desired, and then to continue treatment with dicumarol alone once the prothrombin activity is suitably depressed. Repeated intravenous injections may be difficult technically, and damage to veins may, at times, assume serious importance; heparin injected by any other than the intravenous route is unreliable and may cause pain, swelling, hematomata, and fever. The sublingual route remains to be evaluated. However, heparin has many advantages and may be used alone, especially when dicumarol is contraindicated, or when laboratory facilities for accurate prothrombin time determinations are not available.

Agreement concerning the relative merits of, and the indications for, vein ligation and anticoagulants has not been reached. Each method has advantages and potentialities not posessed by the other. Anticoagulants possess the following advantages: they are usually effective, when properly administered, regardless of the primary seat of thrombosis; they are said to inhibit propagation of clots in diseased veins or of emboli lodged in the pulmonary vessels; they avoid the disadvantages of a surgical procedure, especially in poor risk patients; and they obviate the late effects of vein ligation.

The advantages of vein ligation are: the alleged greater effectiveness in preventing embolism; avoidance of the harmful and even dangerous effects of anticoagulants; its applicability when anticoagulants are contraindicated, as in patients with bleeding diatheses, renal, and liver disease, and in the presence of conditions predisposing to serious hemorrhage, such as active peptic ulcer and ulcerative colitis; the simplicity and brevity of management after it is performed, in contrast to the difficulty of controlling the action of anticoagulants and the troublesome daily tests required when dicumarol or similar substances are used; avoidance of the need for special laboratory facilities, often lacking, and of the

danger involved in delaying emergency surgery required in patients who are receiving anticoagulants.

The following outline has proved useful as a general plan of treatment. Anticoagulants are administered: (1) prophylactically in all conditions in which there is a predisposition to phlebitis, providing surgery is not contemplated; patients with acute myocardial infarction, and those with congestive heart failure confined to bed fall into this group; (2) for the treatment of thrombophlebitis if surgery is not contemplated; in this group will be patients with acute myocardial infarction, congestive heart failure, and other nonsurgical diseases, and postoperative and obstetrical patients in whom the danger of hemorrhage is past; (3) in all patients with phlebitis, including those with pulmonary embolism, in whom vein ligation would be a prohibitive risk; (4) in patients with pulmonary embolism, in whom the seat of venous thrombosis is inaccessible to surgery, or when the evidence is reasonably certain that the emboli come from the heart: (5) when emboli continue to occur despite vein ligation; and (6) when a diagnosis of thromboembolism is suspected, but cannot be established with certainty.

Vein ligation is indicated: (1) for the prevention of pulmonary embolism in elderly patients who are about to undergo major surgery; (2) in all patients with phlebitis and/or pulmonary embolism if surgery is contemplated; (3) for all patients with thrombophlebitis and/or pulmonary embolism in whom anticoagulant therapy is contraindicated; and (4) in patients in whom pulmonary emboli continue to occur, despite apparently adequate anticoagulant therapy.

Summary

The incidence and importance of bland pulmonary embolism as a cause of morbidity and mortality have been emphasized. The pathologic physiology, the clinical picture, the laboratory findings, the diagnosis, and the treatment have been discussed. Venous thrombosis in the lower extremities is the most common immediate cause of pulmonary embolism, but clinical evidence of its presence is frequently lacking. It is difficult to prevent venous thrombosis in spite of the employment of numerous prophylactic measures. Although the diagnosis of pulmonary embolism is easy in some cases, it may be impossible in others. Statistical proof of the effectiveness of treatment is difficult to obtain, but clinical experience appears to indicate that the aforementioned therapeutic procedures are worthwhile. It is evident that many important problems relating to thromboembolism remain unsolved.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Applebaum, E., Bruno, M. S., and Hochstein, E.: Acute Endocarditis as a Complication in Bacterial Pneumonia. J. A. M. A. **148:** 93 (Jan. 12), 1952.

The authors present four cases of bacterial pneumonia complicated by fatal acute bacterial endocarditis. From this small group of cases it is difficult to determine the time of onset of the endocarditis. The authors feel, however, that the inception of the endocardial infection is in the early phase of the pneumonia, probably at the height of the bacteremia. They point out the diagnostic criteria of the endocardial complication which frequently escapes clinical recognition. The valvular lesion in each of these cases was a dynamic aortic regurgitation, the result of early valve destruction. The hazards of inadequate antibiotic treatment are noted, and the authors stress the importance of early diagnosis of the endocardial infection and prompt institution of vigorous antibiotic therapy.

KITCHELL

Friedberg, C. K.: Treatment of Subacute Bacterial Endocarditis With Aureomycin. J. A. M. A. **148:** 98 (Jan. 12), 1952.

The author reports on 11 patients with subacute bacterial endocarditis who were given oral aureomycin. Each case received from 4 to 6 Gm. daily in intermittent doses from five to eight weeks. In six cases the organism isolated from the blood stream was the alpha Streptococcus and in two patients the Streptococcus fecalis. Blood cultures were negative in three patients.

Aureomycin effected a cure in two of the eight patients with positive blood cultures. Five of the six patients who had not recovered with aureomycin were subsequently cured by penicillin or a combination of antibiotics. Aureomycin effected a cure in two of the three patients with negative blood cultures. The sole toxic manifestations of aureomycin were gastrointestinal symptoms which usually came on after prolonged therapy. As a rule aureomycin therapy was followed by prompt clinical improvement; but within three to seven days after stoppage of the drug, fever and positive blood cultures recurred.

These observations supported bacteriologic studies which indicated that the action of aureomycin in the doses given is bacteriostatic and not bacteriocidal. The author believes that aureomycin should be regarded only as an adjunct to penicillin in the treatment of bacterial endocarditis. It is indicated (a) in the treatment of nonhemolytic streptococcal endocarditis which has failed to respond to penicillin; (b) in other forms of endocarditis due to penicillin-resistant organisms, notably penicillin-resistant staphylococci; (c) in endocarditis due to gram-negative bacilli sensitive to this drug; and (d) in combination with other antibiotics when the causative organism is most sensitive to such combinations in vitro.

KITCHELL

Perry, E. L., Fleming, R. G., and Edwards, J. E.: Myocardial Lesions in Subacute Bacterial Endocarditis. Ann. Int. Med. **36:** 126 (Jan.), 1952.

Data on 43 non-penicillin-treated and nine penicillin-treated patients who had subacute bacterial endocarditis were studied, particularly with reference to the microscopic appearance of the myocardium.

Some type of myocardial lesion was found in all except the one case in which the endocarditis was confined to the right side of the heart. The most commonly encountered lesion was the miliary infarct. Other lesions included interstitial and perivascular cellular infiltrates or scars and emboli. Achoff nodules were found in less than 10 per cent of the cases. A foreign body granuloma was present in one of the penicillin-treated series. Aside from this, the individual lesions in the untreated and treated groups were indistinguishable. It is felt that myocardial damage is but one of the several factors operating to bring about myocardial failure in subacute bacterial endocarditis.

WENDKOS

Gulotta, G. A., and Pascucci, S. E.: Subacute Bacterial Endocarditis in a Rheumatic Colony. Bull. St. Francis San. **9**: 43 (Jan.), 1952.

Subacute bacterial endocarditis is of low incidence in the age group of 6 to 16 years in rheumatic colony (0.3 per cent). In those cases in which it is a complication, it always occurs during the active phase of rheumatic disease.

With the newer forms of therapy the intercurrent superimposed infection does not adversely affect the course of rheumatic disease, nor does the antibiotic therapy used in subacute bacterial endocarditis favorably affect the course of rheumatic fever.

BERNSTEIN

BLOOD COAGULATION

Smith, K. S., and Papp, C.: The Prevention of Impending Cardiac Infarction by Anticoagulant Treatment. Brit. Heart J. **13**: 467 (Oct.), 1951.

Impending cardiac infarction is diagnosed when precordial pain changes its character, becomes unrelated to physical effort, and is more frequent and more severe. Rest, sedatives and vasodilators have failed to ward off infarction. Anticoagulants (heparin followed by dicumarol) were tried.

Of 14 persons with impending infarction who were treated with an anticoagulant, six did not develop infarction, and one developed a slight infarct. The authors attribute this favorable course to treatment. The other seven developed severe infarction. Two of three who died showed extensive arterial disease at necropsy. Four developed infarction within three to five days after treatment was begun. The unfavorable results are attributed to the pre-existing widespread coronary arterial narrowing.

SOLOFF

Barker, N. W., Hanson, H. H., and Mann, F. D. Bishydroxycoumarin, Ethyl Biscoumacetate, and 4-Hydroxycoumarine Anticoagulant No. 63. J. A. M. A. **148**: 274 (Jan. 26), 1952.

Like bishydroxycoumarin, the new anticoagulants, ethyl biscoumacetate and 4-hydroxycoumarin (anticoagulant no. 63), induce hypoprothrombinemia, which is of variable degree in different patients. For each drug one-stage determinations of prothrombin time are necessary as a guide to amount and frequency of dose in the individual patient. Ethyl biscoumacetate acts more rapidly and its effect disappears more rapidly when administration is discontinued. These advantages are offset, however, by a greater difficulty in maintainiug the prothrombin time within the therapeutic range.

Anticoagulant no. 63 produces a somewhat more consistent hypoprothrombinemia with less tendency to fluctuations from day to day, but the effect tends to persist for a longer period after administration is discontinued. Vitamin K_1 is a strong antagonist for bishydroxycoumarin and anticoagulant no. 63 and is almost always effective in terminating the hypoprothrombinemia produced by these drugs in 24 to 48 hours. Probably if comparable degrees of therapeutic hypoprothrombinemia are established and maintained, the three compounds will be equally effective in preventing thrombosis, and their use will be attended by the same small risk of bleeding.

KITCHELL

Macht, D. I.: Influence of Some Drugs and of Emotions on Blood Coagulation. J. A. M. A. **148**: 265 (Jan. 26), 1952.

By means of animal experiments and clinical study it is shown that a number of drugs exert thromboplastic or coagulation promoting influences on the blood of animals and human beings. These include the digitaloid drugs and the antibiotics—penicillin, streptomycin, and aureomycin. The well-known and useful mercurial diuretics, the metallic antisyphilitics, amphetamine, and some opium derivatives have the same type of effect. Of no less importance is the discovery that even in healthy persons of both sexes, acute apprehension, fear and intense worry markedly accelerate blood coagulation and therefore call for suitable psychologic as well as pharmacologic therapy.

There is usually a wide margin of safety for accommodating fluctuations in coagulation time of the blood, but the thromboplastic properties of our most useful medicaments should be borne in mind and prevented, in certain cases, from exerting deleterious effects by the administration of suitable anticoagulant agents. The author points out that all the glycocides of digitalis (whether from Digitalis purpurea or from Digitalis lanata) produced a more or less powerful coagulating effect on blood.

KITCHELL

Loomis, T. A., Jesseph, J. E., and Beyer, R. E.: Prolongation of the Anticoagulant Action of Heparin with Procaine and Butacaine Conjugates. J. Pharmacol. & Exper. Therap. **104**: 87 (Jan.), 1952.

The relatively brief duration of the anticoagulant action of heparin constitutes one of the principal

undesirable factors in its use clinically. The authors describe the preparation of butacaine-heparin and procaine-heparin conjugates which were found to decrease the absorption of heparin. The intramuscular administration of aqueous suspensions of these conjugates in dogs resulted in a 24-hour duration of anticoagulant action. With the doses employed there was some evidence of procaine toxicity but none of butacaine toxicity. Although heparin in gelatin-dextrose menstruum showed a longer duration than with control aqueous heparin, neither preparation resulted in anticoagulant action longer than 16 hours.

SAGALL

CONGENITAL ANOMALIES

Humphreys, G. H., II: Surgical Revision in Congenital Cardiovascular Disease. Bull. New York Acad. Med. **28**: 28 (Jan.), 1952.

The author presents a practical classification of congenital cardiovascular anomalies, dividing them into three major groups: (I) those which represent a postnatal persistence of a vascular or intracardiac pattern which is normal at some stage in fetal life (a failure in normal involution); (II) those which result from the abnormal involution of structures which normally persist, or combinations of these with group I anomalies; and (III) those in which the course of development is abnormal from the very beginning.

If the various specific disorders are considered in terms of the above groups and also in chronologic order of fetal development, certain generalizations become apparent. The prognosis is better, the later the stage in fetal development which the anomaly represents. Group I and Group II anomalies whose origin does not precede that of the 12 mm. embryo either cause little physiologic disturbance or are correctable by surgery. Group III cases mainly represent those which originate earlier than the 7 mm. embryo, and little surgical help is at present available for them.

Lesions producing deep or constant cyanosis originate very early and cannot be corrected. Lesions producing variable, inconstant, or late-appearing cyanosis originate later in embryonic life, and some physiologic improvement may be obtained by surgical methods even though a normal anatomic pattern is not restored. The present status of the surgical revision of various congenital anomalies is reviewed and discussed.

SAGALL

Van Lingen, B., McGregor, M., Kaye, J., Jacobs, H. D., Braudo, J. L., Bothwell, T. R., and Elliott, G. A.: Clinical and Cardiac Catheterization Findings Compatible with Ebstein's Anomaly of the Tricuspid Valve: A Report of Two Cases. Am. Heart J. **43**: 77 (Jan.), 1952.

The authors present two cases whose clinical findings are consistent with the diagnosis of Ebstein's anomaly of the tricuspid valve. In this anomaly, the displaced tricuspid valve divides the right ventricle into two parts and causes the proximal portion to be continuous with the cavity of the right atrium. The clinical manifestations of the two patients (both women, 20 and 22 years of age) included delayed onset of cyanosis, enlarged heart, poor heart sounds, and mid-diastolic murmurs to the left of the sternum; and radiologic study showed a markedly enlarged hypoactive right ventricle, normal or diminished pulmonary arteries, and normal pulsations of the left ventricle. The electrocardiogram showed right bundle branch block and low voltage. Cardiac catheterization showed normal pulmonary artery pressure, and a higher systolic and mean pressure in the distal part of the right ventricle than in the proximal part. The pulse contours from the right ventricular cavity had a gradual rise and fall during systole in the distal part of the right ventricle, and an abbreviated diastolic plateau. There was evidence of a defect in the auricular septum, with flow from left to right at rest, and reversal during exercise. The authors consider the catheterization data compatible with the division of the right ventricle into two functionally separate chambers by a displaced tricuspid valve, justifying the first reported *in vivo* diagnosis of Ebstein's anomaly of the tricuspid valve.

HELLERSTEIN

Bing, R. J.: Congenital Heart Disease. An Introduction and Classification. Am. J. Med. **12**: 77 (Jan.), 1952.

The author provides a concise orientation to the field of congenital heart disease and a new classification system based upon alterations in cardiovascular physiology. Congenital heart malformations are separated into three groups. The first category includes cardiac malformations in which the pulmonary flow is less than the systemic blood flow and the pulmonary artery pressure is usually decreased. The systemic flow is defined as the volume of venous blood which returns to the right auricle.

In the second category the pulmonary flow is greater than the systemic flow and the pulmonary artery pressure is normal or increased. The third category includes those conditions in which the pulmonary flow equals the systemic flow at rest and after exercise.

The author discusses each clinical entity briefly. Careful evaluation, inspection, and physical examination may clarify the diagnosis in congenital heart disease. Cardiac catheterization and angiocardiography are important supplements to the clinical and radiologic diagnoses of these malformations.

HARRIS

Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Ebstein's Disease: Report of the First Case Diag-

nosed during Life. Am. J. M. Sc. **222:** 554 (Nov.), 1951.

The clinical diagnosis of Ebstein's anomaly with an associated interatrial septal defect was confirmed by angiocardiography for the first time in a living patient. Although the patient was hypertensive, there were many unusual features leading to the suspicion of a congenital cardiac defect.

The patient was a 34 year old female with known hypertension. She had experienced symptoms of dyspnea and palpitations in the past and had been treated with some improvement on a salt-poor regimen. The heart was markedly enlarged, with a systolic precordial murmur heard best in the left third intercostal space. Radiographic studies disclosed right and left heart enlargement with marked posterior and anterior protrusions. There was prolonged right heart circulation, arterial oxygen unsaturation (82 per cent) and polycythemia. The electrocardiogram revealed giant P waves and right bundle branch block.

Using the biplane stereoscopic angiocardiographic unit, which permits simultaneous right-angle exposures at a rate of two per second on roll film, the authors were able to identify a case of Ebstein's anomaly. Diodrast solution was followed, by means of films taken at one-half second intervals, into a huge right atrium where an atrial septal defect was identified, and into another anterior inferior chamber which was partially demarcated from the auricle. This was thought to represent the "auricularized" right ventricle which is produced by the downward and mesiad displacement of the anomalous tricuspid valve. The oblique views then show the dye entering the functioning portion of the right ventricle, separated from the adjacent chamber by a narrow band which never becomes opacified. The separation probably represents the tricuspid valve. The pulmonary artery contour and the left cardiac chambers were not demonstrable.

SHUMAN

Glover, R. P., Bailey, C. P., O'Neill, T. J. E., Downing, D. F., and Wells, C. R. E.: The Direct Intracardiac Relief of Pulmonary Stenosis in the Tetralogy of Fallot. J. Thoracic Surg. **23:** 14 (Jan.), 1952.

After pointing out that the various shunts devised in the treatment of the tetralogy of Fallot are in effect the production of a "patent ductus arteriosus," the authors attempted to relieve the pulmonary obstruction in this condition by a more direct intracardiac approach. Thirty patients were treated in this manner.

In 15 cases pulmonary valvular stenosis was found at the time of operation and incision of the valve was performed. There were two operative deaths, while a third died 13 weeks postoperatively.

In 12 patients an obstructing malformation of the pulmonary conus region was present, and in four of these death occurred during the operation. In the remaining three cases a localized constriction of the pulmonary artery was found, distal to normal pulmonary valve. The introduction of graduated sounds seemed to accomplish a most satisfactory enlargement of the arterial lumen.

The mortality rate for the entire series was 23.3 per cent which compared favorably with a figure of 22 per cent reported in the case of treatment of pulmonary stenosis by means of systemic artery–pulmonary artery shunt.

ABRAMSON

Dagonet, Y.: Anomalies of the Origin of Coronary Arteries. Report of an Observation on Abnormal Origin of the Left Coronary Artery. Arch. mal. coeur **45:** 7 (Jan.), 1952.

The author reports the case of a 3 months old infant who started to vomit 10 days after birth and became severely dyspneic. The diagnosis of aberrant origin of the left coronary artery from the pulmonary artery was established on the basis of the findings of marked cardiac enlargement and an electrocardiographic pattern of anterior wall infarction. The diagnosis was confirmed at autopsy.

Following a review of the literature the author concludes that the following three findings are characteristic for this anomaly: Reduced state of nutrition due to difficulties in feeding since every attempt to swallow apparently precipitates anginal pain; globular enlargement of the heart; and the typical electrocardiogram. Death usually occurs in the fourth month of life. Autopsy invariably reveals an enlarged heart due sometimes to tremendous dilatation of the left ventricle. The main histologic changes are found near the ventricular cavity and consist of thickening of the endocardium and various stages of necrosis and fibrosis of the myocardium. Since survival to 65 years due to development of sufficient collateral circulation has been reported, the author believes that the condition could be corrected by surgical approach, for example, an anastomosis of the left internal mammary artery to the left coronary artery.

PICK

Smith, R. W.: Circulatory Factors Affecting Anesthesia in Surgery for Congenital Heart Disease. Anesthesiology **13:** 38 (Jan.), 1952.

The author has outlined the chief anatomic and physiologic alterations in patients with patent ductus arteriosus, tetralogy of Fallot and coarctation of the aorta. The special problems, especially as they concern the anesthetist, in these various types of patients are pointed out and explained.

The main hazards encountered during operations for congenital cardiac lesions result principally from altered hemodynamics and anoxia, rather than from cardiac irritability and arrhythmias.

SAGALL

Fuller, J., Taylor, B. E., Clagett, O. T., and Wood, E. H.: Blood Pressure in the Aorta During Resection, and Repair of Coarctation of the Aorta. J. Lab. & Clin. Med. **39**: 10 (Jan.), 1952.

During nine operations for the surgical repair of coarctation of the aorta in man, a mobile oscillographic camera was used to make simultaneous recordings of the electrocardiogram, respiration, heart rate and direct blood pressure in the radial artery, and in the aorta above and then below the site of stricture before and after resection, and of end-to-end anastomosis of the aorta.

The average systolic and pulse pressures in the radial artery exceeded the simultaneously recorded pressures in the proximal aorta, but the radial diastolic and mean pressures averaged less than the pressures for the same heart beat in the aorta proximal to the stricture. The systolic, diastolic, pulse and mean pressures in the aorta distal to the stricture averaged 41 mm. of mercury less than the simultaneously recorded radial arterial pressures. Occlusion of the site of the coarctation produced no change in pressure in the proximal or distal aorta. When the left subclavian artery was occluded, an increase in proximal aortic pressure was produced and, in spite of the increased central arterial pressure, there was a decrease in distal aortic pressure. Opening of the anastomosis produced an immediate decrease in proximal aortic pressure and an increase in distal aortic pressure. It was therefore evident that certain mechanical hydrodynamic factors play an important role in the genesis of the hypertension which exists in this condition.

Direct studies of radial and femoral arterial pressure carried out before and after operation on these patients also showed a change toward the normal state.

MINTZ

Abrahams, D. G., and Wood, P.: Pulmonary Stenosis with Normal Aortic Root. Brit. Heart J. **13**: 519 (Oct.), 1951.

The authors analyze 71 instances of pulmonary stenosis, excluding Fallot's tetralogy, five of which were confirmed at necropsy and 10 at operation. The following classification is offered:

1. Simple pulmonary stenosis (45)

(a) valvular (37): mild cases, in which right ventricular pressure is less than 26 mm., have no symptoms. The severe ones with pressures greater than 39 mm. may have dyspnea on effort. The x-ray in this group shows enlargement of right ventricle, poststenotic dilatation of pulmonary artery, and an ischemic lung. The electrocardiogram varies from normal to right bundle branch block. Catheterization shows the mean and systolic right ventricular pressures higher than those of the pulmonary artery. The cardiac output is low in severe instances and the arteriovenous oxygen difference is increased.

(b) infundibular (8): have (*i*) no parasternal left; (*ii*) a lower position of the thrill; (*iii*) no poststenotic dilatation; (*iv*) three pressure zones.

2. Pulmonary stenosis with arteriovenous shunt (15)

(a) aorta-pulmonary: this type was not present in this series.

(b) interventricular (8): catheterization revealed the left to right ventricular shunt and a right ventricular pressure higher than that of the pulmonary artery.

(c) interatrial (7): catheterization reveals the shunt.

3. Pulmonary stenosis with veno-arterial shunt (9)

(a) interventricular (1): this type is indistinguishable from Fallot's tetralogy unless a reversal of flow had been observed at another time.

(b) interatrial (8): pulmonary stenosis must be severe. Diagnosis is made by catheterization or angiocardiography.

4. Acquired pulmonary stenosis

(a) from occlusive pulmonary artery disease (1)

(b) from compression of the pulmonary artery (1)

Instances of pulmonary stenosis form 12 per cent of all congenital heart disease. Mild cases may live to middle or old age. Severe ones are likely to die of failure in the second or third decade. Ten of these 71 had pulmonary valvulotomies. Three died and seven appear to have done well. More recently, 17 pulmonary valvulotomies have been done with no mortality.

SOLOFF

CONGESTIVE HEART FAILURE

Cossio, P.: Ligation of the Vena Cava in the Treatment of Heart Failure. Am. Heart J. **43**: 97 (Jan.), 1952.

The author reports the results of ligation of the inferior vena cava below the renal veins in 90 patients with severe and uncontrollable heart failure. The ages ranged from 27 to 67 years. Thirty-five had rheumatic heart disease, usually polyvalvular; 48 had arterial hypertension with or without coronary arteriosclerosis; five had syphilitic aortic regurgitation; and two had interauricular septal defects. The surgical mortality of the first 20 patients was 25 per cent, and in the last 70 patients was 6 per cent. In 63 of the 81 surviving patients, there was appreciable improvement in the early postoperative period, that is, relief of orthopnea, and diminution of liver congestion, edema, ascites, and heart size. Months later, the benefit persisted in 51 of these 63 patients, that is, 56.7 per cent of the total. The improvement was maintained, provided the patients continued medical treatment for heart failure, though in most cases not so strictly as prior to operation. The most lasting and surprising recoveries were made by patients with recurrent

paroxysmal dyspnea, hemoptysis, and signs of phlebothrombosis in the legs. The author suggests that ligation of the vena cava eliminates the source of microemboli which show no manifest clinical features but which may be a contributory cause of persistent heart failure.

HELLERSTEIN

Silverman, J. J., and Worthen, J. F.: Agranulocytosis in a Patient Treated with Mercurial Diuretics. J. A. M. A. **148:** 200 (Jan. 19), 1952.

An unusual depression of the white blood cells is reported in a patient under treatment for congestive circulatory failure with mercurial diuretics. Meralluride injection was believed to be responsible for this reaction which was not observed following the use of mercaptomerin sodium. The peripheral blood was characterized by severe neutropenia at the height of the disorder, and the bone marrow by a maturation arrest of the granulocyte series at the myelocyte stage. The mercurial diuretics should be added to the list of drugs capable of producing agranulocytosis.

KITCHELL

Peters, J. P.: Problem of Cardiac Edema. Am. J. Med. **12:** 66 (Jan.), 1952.

The author reviews the problem of cardiac edema, referring to the physiologic principles that govern water metabolism, control of water and salt exchanges in normal subjects, and the forces responsible for the production of transudation and edema in analogous states. The maintenance of fluid volume and distribution within the body depends upon the exchange of water between the body and its environment as well as the exchange of water within the body itself. The sense of thirst and the kidneys are responsible for regulation of water exchange between the body and the environment.

The strongest stimulus to thirst is the effective osmotic pressure of extracellular fluid of which the sodium salts are the most important constituent. The effective osmotic pressure also determines the state of cellular hydration. The integrity of the internal environment depends upon the regulatory function of the kidney. The kidney can conserve water by maximum reabsorption of water as well as by maximum reabsorption of sodium salts which permits further reabsorption of water. The posterior pituitary gland controls the terminal reabsorption of water from the renal tubules. The gland behaves as if its activity were controlled by the effective osmotic pressure of the serum and the state of cellular hydration. The agent governing the reabsorption of sodium chloride, although identified with the adrenal cortical hormone, has not been precisely defined as yet. The stimulus may be the volume of fluid in the body.

Edema formation involves an increase of the total amount of body water and displacement of this fluid into the extravascular space. Salt retention provokes water retention but edema does not result if the circulation system is intact. Cardiac edema is governed by the forces controlling the exchange and disposition of fluid in other conditions. The author concludes that the conventional Starling theory of the formation of cardiac edema is more logical than the forward failure theory.

HARRIS

Décourt, L. V., Tranchesi, B., Barbato, E., and Macruz, R.: Respiratory Volume and Pulmonary Engorgement in Congestive Heart Failure. Arq. brasil. cardiol. **4:** 391 (Dec.), 1951.

The authors describe the changes observed in lung volume, vital capacity, and maximal breathing capacity in patients with congestive heart failure during basal conditions and following a standard exercise sufficient to cause dyspnea. The majority of patients had rheumatic mitral valve disease, since the purpose of the investigation was the study of the role of pulmonary congestion in the genesis of exertional dyspnea. There was a definite increase in the volume of tidal air in most instances following exercise. Vital capacity, which was markedly reduced at rest, usually increased after exertion. The maximal breathing capacity, which was extremely low at rest, increased sharply following exercise.

It is concluded that effort dyspnea is not related to the degree of pulmonary engorgement, and that the respiratory capacity does not reflect the intensity of passive congestion of the lungs. The authors suggest that metabolic and reflex phenomena are probably more important factors in this type of dyspnea.

SCHLESINGER

Hoffman, T.: Surgical Treatment of Heart Failure by Ligation of the Inferior Vena Cava. Deutsche. med. Wchnschr. **51:** 1624 (Dec.), 1951.

Following a discussion of pathophysiologic effects of ligation of the inferior vena cava in congestive heart failure, the author reports the results of the operation performed in the Hospital Broussais in Paris on 60 cases. The material consisted of 44 cases with mitral valvulitis, 12 cases of hypertension, two cases of aortic stenosis and two cases with signs "of marked myocardial damage."

The over-all mortality was 11 per cent. Four cases died of postoperative hemorrhage (two of them while treated with heparin), three of cardiac arrest during surgery. Four others died within four months of various causes probably associated with the operation (nephritis, hemiplegia, recurrence of polyarthritis).

All cases, who were bedridden and resistent to the usual therapy prior to operation, showed, with one exception, improvement following surgery, which, however, was only transient in four. Fifteen were

able to perform restricted activities and 25 returned to their original occupation. In the author's experience, the operation is contraindicated only in younger individuals with active rheumatic carditis and in persons over 65 years.

PICK

Richter, C. P.: The Physiology and Cytology of Pulmonary Edema and Pleural Effusion Produced in Rats by Alpha-Naphthyl Thiourea (ANTU). J. Thoracic Surg. **23:** 66 (Jan.), 1952.

The authors described methods of evaluating the changes occurring in the lungs of Norway rats after the use of alpha-naphthyl thiourea to produce pulmonary edema. The chemical was given intraperitoneally in varying doses to a total of 203 animals, and quantitative methods were used for the measurement of the fluid in the lungs and in the pleural cavities. The pulmonary edema began to form within the first hour after injection, reaching a maximum during the second to the fourth hours. The pleural effusion began to appear after the first hour and continued to increase for the next 6 to 10 hours.

It was found that after poisoning with the chemical, most of the material filling the lungs and pleural cavities came from the extracellular fluid of the blood. After leaving the lung capillaries, the edema fluid was believed to flow through the interalveolar spaces into the lymph ducts. Fluid also was present in large amounts in the perivascular spaces. Since it left the capillaries faster than it could be removed by the lymph ducts, the fluid was forced to flow either into the alveoli or in the lymph ducts to the pleura. With the contraction of the lungs with each expiration, the material was squeezed out into the alveolar spaces and the pleural cavities.

On the basis of his results, the author concluded that his method of measuring quantitatively the amount of pulmonary edema and pleural effusion could be applied to testing the effects of various agents, such as morphine, atropine and sympathectomy, in the treatment of these pathologic states.

ABRAMSON

Horst, H. G.: The Question of Neurogenic Pulmonary Edema in Epileptics. Aerztl. Wchnschr. **7:** 35 (Jan.), 1952.

The author observed the onset of typical pulmonary edema following an epileptic seizure in two cases. The findings of the cardiovascular system were normal in both, with the exception of sinus tachycardia and slight transitory flattening of the T waves in the limb lead electrocardiogram in one. Since the onset of acute pulmonary congestion could not be explained on the basis of heart failure, the author believes that a neurogenic mechanism similar to that operating in animals, in which fatal pulmonary edema has been produced by suboccipital injection of Veratrine, may be responsible. The deposition of this powerful sympathicotropic agent near the central nervous system produces dilatation in rabbits and increase of permeability of small lung vessels and, consequently, redistribution of blood from the systemic towards the pulmonary circulation.

PICK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Cole, S. L., and Sugarman, J. N.: Cerebral Manifestations of Acute Myocardial Infarction. Am. J. M. Sc. **223:** 35 (Jan.), 1952.

Symptoms referable to the central nervous system including syncope, convulsions, coma and hemiplegia may dominate the clinical picture in acute myocardial infarction. Six patients with such manifestations are presented to show that the cardiac process may be overlooked when associated with cerebral symptomatology. Autopsy was performed in five and disclosed no evidence of cerebral thrombosis, embolism or hemorrhage in the head examinations. An additional 15 patients are presented in whom autopsy had revealed combined myocardial infarction and cerebrovascular accident.

The authors suggest that generalized cerebral manifestations in the former cases may be induced by ischemia and anoxia following a drop in blood pressure associated with coronary occlusion. Focal neurologic findings may be the result of segmental narrowing and arterial insufficiency produced by cerebral arteriosclerosis. An attempt is made to differentiate the picture of acute myocardial infarction with central nervous system symptoms from the combined lesions of brain and heart.

SHUMAN

Ströder, U.: Contribution to the Diagnosis and Therapy of Coronary Disease with Hydrergin. Cardiologia **19:** 127 (Fasc. 2), 1951.

The author presents two cases of angina pectoris with typical electrocardiographic changes in an exercise tolerance test. The electrocardiograms remained unchanged when the test was repeated following intramuscular injection of 0.3 mg. of Hydrergin, although no pain was noted. However when the patients were treated for several days with oral doses (3 to 5 drops) of a Hydrergin solution, and then the exercise tolerance test was repeated following the same intramuscular injection, both pain and electrocardiogram changes were absent. In a third case of essential hypertension, with anginal pain and multiple premature beats on exertion, the symptoms disappeared after oral treatment with Hydrergin.

The author concludes that the use of the ergot preparation is not reliable in differentiating positive results of exercise tolerance tests on organic and functional bases. The cases demonstrate that

anginal pain and ectopic rhythms due to coronary disease may respond well to oral therapy with Hydrergin.

PICK

Keys, A.: Cholesterol, "Giant Molecules," and Atherosclerosis. J. A. M. A. **147:** 1514 (Dec. 15), 1951.

The author points out that there is substantial correlation between the concentrations in human blood serum of total cholesterol and the "giant molecules" characterized in the ultracentrifuge by −10 to −20 Svedberg Units of sedimentation (G substances). After examination of all available data, he concludes that there is no evidence showing that the concentration of G substances is more critical than that of total cholesterol.

He points out that neither measurement is a good discriminator between persons with coronary disease and healthy persons, although both G and total cholesterol show distinct tendencies toward elevation in the serum of persons with coronary disease. If there is any advantage to one of these measurements over the other in detecting or predicting coronary disease, the evidence is in favor of total cholesterol determinations. There is no evidence that a level of G concentration in the blood would be of practical value as an indicator of the probability of present or impending coronary disease.

KITCHELL

Vineberg, A.: Treatment of Coronary Artery Insufficiency by Implantation of the Internal Mammary Artery into Left Ventricular Myocardium. J. Thoracic Surg. **23:** 42 (Jan.), 1952.

After demonstrating experimentally that the internal mammary artery could be successfully implanted into the walls of the left ventricle, the authors performed the operation on four patients with coronary insufficiency. Three survived the procedure while one died 60 hours after surgery. In the latter case a postmortem examination revealed a patent internal mammary artery, but there was a recent thrombosis of the anterior descending branch of the left coronary artery. In the case of the other three patients, one was well and working at the end of five months, while the others showed some improvement. The authors obtained no evidence that the procedure caused any harm to the existing circulation.

The rationale for the operation was the experimental evidence that new arterial branches were formed in the myocardium at the site of implantation, which anastomosed with the left coronary artery. Thus the heart was protected against death by infarction in the event that the anterior descending branch of the left coronary artery subsequently became occluded.

ABRAMSON

Fish, C. A., and Grantham, E. G.: Relief of Pain in Acute Myocardial Infarction by Procaine Block of the Sympathetic Nerve Supply. Ann. Int. Med. **36:** 172 (Jan.), 1952.

A patient with severe pain resulting from an acute myocardial infarction was not afforded any relief from opiates, nitroglycerine or oxygen but did obtain immediate and sustained analgesia following procaine infiltration of the left stellate ganglion. The benefits from this procedure are ascribed to inhibition of afferent pain-conducting fibers which pass through the sympathetic ganglion, rather than to alterations of coronary blood flow resulting from a block of sympathetic efferent fibers supplying the walls of the coronary arteries.

WENDKOS

ELECTROCARDIOGRAPHY

Segers, M., Regnier, M., and Delatte, E.: Sudden Appearance of the Electrocardiographic Pattern of Preponderance. Acta cardiol. **7:** 63 (Fasc. 1), 1952.

The authors present eight examples of sudden change of the electrocardiogram to the pattern of "left ventricular preponderance." With the exception of one case with aortic valvulitis, all had clinical evidence of arteriosclerotic heart disease with or without myocardial infarction. The changes of the electrocardiogram occurred during sinus rhythm and consisted of an alteration of the direction of the QRS and T axis, or in alternation of a bundle branch block pattern with complexes resembling those of heart strain. In two instances such changes were also seen in the precordial leads.

The authors believe that positional factors and ventricular premature beats, leading to ventricular fusion beats, can be definitely ruled out. They ascribe the phenomenon to the intermittent appearance of intraventricular block. They conclude that ventricular preponderance in the electrocardiogram is "the consequence of a peculiar intraventricular block and not of ventricular hypertrophy."

PICK

Simonson, E.: Effect of the Change from Supine to Sitting Position on the Chest Leads. Am. Heart J. **43:** 53 (Jan.), 1952.

The author has made a statistical analysis of the electrocardiographic changes from the supine to the sitting position in V_2, V_6, and V_6R of 23 healthy men. The mean differences of the QRS and T amplitudes were small or absent. In view of the absense of significant positional changes, the sitting position can be used in bedridden patients and for taking back leads.

HELLERSTEIN

Foster, R. F., and Layman, J. D.: Generalized Urticaria with Electrocardiographic Changes Simulating Myocardial Infarction. J. A. M. A. **148:** 203 (Jan. 19), 1952.

The authors report a case in which electrocardiographic findings suggested myocardial infarction associated with drug-induced urticaria. Electrocardiographic tracing taken on the second day after admission to the hospital indicated complete auriculoventricular dissociation. The QRS intervals measured 0.12 second with pronounced deformity. The T waves in lead II were monophasic and in leads III and IV inverted. Q waves were noted in leads I and III.

Electrocardiographic diagnosis was third-degree heart block with dissociation of auricles and ventricles, and intraventricular block with features suggesting myocardial infarction, posterior type, atypical. The clinical diagnosis was painless coronary occlusion. These electrocardiographic findings disappeared in 12 days; it is concluded this condition was not myocardial infarction but a manifestation of a cardiovascular allergic reaction.

KITCHELL

Schmidt, J.: Studies on the P wave of the Electrocardiogram. III. The P Cardiale. Ztschr. Kreislaufforsch. **41:** 10 (Jan.), 1952.

The author describes an abnormal type of P waves which, in his opinion, is characteristic of pathologic changes in both auricles. In contrast to previously described patterns associated with isolated anomalies of either auricle ("P dextro- and sinistrocardiale") this pattern is termed by the author "P cardiale." The characteristics are widened (> 0.10 second) and biphasic auricular deflections, consisting of right precordial leads of a narrow initial portion, representing right auricular activity, and a broad and inverted portion (activation of the left auricle); in other precordial leads and in the limb leads the P wave is notched and double peaked. The distance between the two peaks measures at least 0.03 second, indicating dissociation of auricular activation due to inter-auricular block.

P waves of the described type are found in primary disease of the left heart with secondary involvement of the right side, and in combined lesions affecting from the beginning both sides of the heart. The "P cardiale" is not a permanent alteration of the electrocardiogram and may disappear with improvement of the cardiac condition.

PICK

Griffith, G. C., and Herman, L. M.: Persistent Complete Heart Block in Diphtheritic Myocarditis. J. A. M. A. **148:** 279 (Jan. 26), 1952.

The development of complete heart block in diphtheritic myocarditis usually foretells a fatal outcome. When the patient does survive, the conduction defect usually disappears rapidly. The authors report a case of diphtheritic myocarditis with autopsy findings. The unusual features are: (1) variations in the conduction and irritability of the heart continuing for many months after the acute process; (2) persistent clinical evidence of myocarditis, namely, low voltage of QRS complexes, arrhythmia, and chronic congestive failure; and (3) survival for 12 months despite a complicating hepatitis, with death eventually from sudden cessation of heart beat—a direct result of the diphtheritic damage. The autopsy findings showed a relatively small amount of degenerative change in the myocardium.

KITCHELL

Himmelstein, A., and Scheiner, M.: The Cardiotrachoscope. Anesthesiology **13:** 62 (Jan.), 1952.

The authors describe an instrument which gives a continuous visual image on cathode ray tubes of the electrocardiogram and pulse rate, and is designed for use during surgery. The instrument can operate continuously for hours or days. It can be placed clear of the operating field. An alarm mechanism is so arranged that either a warning light or an audible signal is set up if the heart rate falls above or below preset levels, and will warn immediately if cardiac arrest occurs.

SAGALL

Regnier, H., and Taccardi, B.: The Variations of the Frontal Vectorcardiogram as Function of the Used Leads. Acta cardiol. **7:** 20 (Fasc. 1), 1952.

In 10 normal persons and in 10 patients with various types of heart disease frontal vectorcardiograms of ventricular activation were recorded according to the methods of Wilson and Johnston, Donzelot and Milanovich, and Duchosal and Sulzer. The direction of the main axis of the QRS loop and the direction of successive instantaneous vectors, as obtained with the three methods, were compared and the differences tabulated.

Contour, orientation and direction of development of the vector loop may vary considerably in the same subject depending on the system of application of the electrodes. This holds for normals as well as for abnormal tracings, the differences being more marked in the latter. Bipolar and unipolar limb leads frequently do not correspond the projection of the vector loop upon the respective axes.

The differences in the results obtained with the various systems are due to a number of factors, the more important being the relatively large size of the heart with respect to that of the conductor, and the fact that, in the three methods employed, the electrodes are situated at unequal distances from each other and from the heart. Knowing these variations of the normal and abnormal vectorcardiogram is important in providing a more exact interpretation of the curves, from the physiologic as well as from the clinical point of view.

PICK

Taran, L. M., and Szilagyi, N.: Technical Considerations in the Measurement of the Electrical Systole (Q-T Interval) and Its Relationship to the Electrical Events in the Cardiac Cycle. Bull. St. Francis San. **9:** 15 (Jan.), 1952.

The first of a series of studies aimed at clarification of some of the usual errors made in the measurement of the electrical systole (Q-T interval) is presented in this paper. Problems involved in the measurement of the Q-T interval in electrocardiographic tracings in which T and P overlap, due to a prolongation of the Q-T interval at a rapid cardiac rate or due to a prolongation of both the P-R and Q-T intervals, have been discussed. A procedure is presented for differentiating the T and U waves in tracings of unusual pattern. This procedure offers a high degree of stability and accuracy in the measurement of the electrical systole (Q-T interval).

This study points up the observation that failure to adhere to a critical technic in regard to the recognition of the end of the T wave may account for the wide divergence of results in the measurement of the Q-T interval in acute heart disease reported in the recent literature. This error in technic may in part be responsible for the discordance of opinion concerning the clinical value of this measurement in acute heart disease.

BERNSTEIN

ENDOCRINE EFFECTS ON CIRCULATION

Birkhill, F. R., Corrigan, K. E., and Hayden, H. S.: The Metabolism of Radioactive Iodine (I^{131}) in Patients with Cardiac Disease. Am. J. Roentgenol. **67:** 42 (Jan.), 1952.

This investigation was instituted to determine the effects of varying degrees of cardiac failure upon thyroid concentration of administered I^{131}. Twenty patients with heart failure showed increased concentration of I^{131} in the tissues of the thighs and the liver at the end of 24 to 36 hours as compared with those without heart failure; the I^{131} concentration over the thyroid in these cases was correspondingly diminished. The study therefore indicates that in the presence of congestive failure I^{131} uptake over the thyroid gland may be borderline and may mask the presence of thyrotoxicosis. In still other situations the existence of occult edema may be detected by I^{131} tracer studies over the thighs and the liver before clinical manifestations appear.

SCHWEDEL

HYPERTENSION

Restall, P. A., and Smirk, F. H.: Regulation of Blood Pressure Levels by Hexamethonium Bromide and Mechanical Devices. Brit. Heart J. **14:** 1 (Jan.), 1952.

This paper is concerned with the circulatory effects of hexamethonium bromide in man. Hexamethonium bromide produces (1) a fall in venous pressure in individuals with and without congestive failure, (2) an increase in leg volume of 15 to 80 ml. per 2000 cc. of limb in eight observations, (3) no drop in limb temperature, and (4) a drop in blood pressure greater for the systolic pressure and greatest in the erect position.

These effects could be neutralized by immersing a subject up to his chin in water, and could be potentiated by enclosing the subject up to his nipples in an air pressure chamber that was subjected to suction so as to produce negative pressure.

With much larger doses of hexamethonium bromide, a drop in pressure could be obtained which was equal in the erect and horizontal positions and could not be neutralized by immersion.

The greatest effect of the drug is attributed to a decreased capacity of the vessel walls of the dependent parts to contract and thereby resist gravity pressure dilatation. Peripheral resistance is decreased and is not abolished by mild exercise, meals or emotions.

SOLOFF

Kilpatrick, John A., and Smirk, F. H.: Comparison of Oral and Subcutaneous Administration of Methonium Salts in the Treatment of High Blood Pressure. Lancet **6697:** 8 (Jan.), 1952.

To produce therapeutic falls in blood pressure, much larger doses of hexamethonium bromide are needed by the oral than by the subcutaneous route. The effects of oral administration continue longer, but in most patients they are less predictable from one occasion to another. Symptoms of intolerance develop in a large proportion of patients when effective doses are given by mouth. Oral therapy is more likely to be successful when the subcutaneous dose needed to control blood pressure is small.

Patients whose blood pressure reduction is inadequate or who have important side-effects from oral hexamethonium bromide should be maintained on the insulin-like regimen of subcutaneous hexamethonium bromide. The best results can be obtained only by adjusting the dose, times of administration, and mode or modes of administration in terms of whole-day observations of the patient's response. Failure to ameliorate hypertensive manifestations with hexamethonium salts is usually due to a defect in technic.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Moia, B., Malinow, M. R., and Bandino, C.: Segmentary Studies of Venous Pressure in Man in the Course of Catheterization. Acta cardiol. **7:** 1 (Fasc. 1), 1952.

The authors studied changes of the venous pressure occurring during stepwise retraction of a cardiac catheter from the right atrial cavity to the cubital vein. In three cases with heart disease without heart failure, in three cases with chronic pulmonary disease

ıd in nine normals, the auricular pressure never ceeded 60 mm. of water; in five of them it remained nchanged throughout the whole pathway of the atheter, and in 10 it was 20 to 50 mm. higher distal o the axillary vein. Following deep inspiration the ressure dropped in the central part of the venous ystem in the majority of observations. Compression f the abdomen increased central and peripheral pres- ıre by not more than 20 mm.

In a second group of six cases with right heart ailure, intra-auricular pressure was always higher han 70 mm. water. In half of the cases it diminished lightly, in the other half it increased, when the atheter reached the level of the arm. Deep respira- tion always increased the central venous pressure nd, in two cases of this group, the peripheral pres- sure. Pressure on the abdomen increased both by more than 20 mm.

The authors conclude that under normal condi- tions, in supine position, the peripheral venous pres- sure is independent of the height of right atrial pres- sure, and that no progressive pressure gradient exists between peripheral and central venous seg- ments. In patients with cardiovascular or chronic pulmonary disease without right heart failure, the conditions are similar to those found in normals.

PICK

Carlens, E., Hanson, H. E., and Nordenström, B.: Temporary Unilateral Occlusion of the Pulmonary Artery. A New Method of Determining Separate Lung Function and of Radiologic Examinations. J. Thoracic Surg. **22:** 527 (Nov.), 1951.

In an attempt to devise a means of determining the functional state of the lungs individually, the authors occluded the pulmonary artery on one side in a series of dogs and in three human subjects. This was accomplished using a cardiac catheter provided with an inflatable balloon.

Ten experiments were performed on eight dogs, and in no case were any complications noted follow- ing unilateral occlusion of the pulmonary artery. Similar results were noted in the three patients.

It was suggested that the method had promise in the preoperative evaluation of patients to be sub- jected to pneumonectomy, as well as in the radio- logic visualization of one pulmonary artery at a time using Diodrast.

ABRAMSON

Whittlesey, R. H.: Dynamic Changes in Arterial Pressure Pulses Produced by a Simulated Sac- cular Aneurysm. Am. J. Physiol. **168:** 192 (Jan.), 1952.

A saccular aortic aneurysm was imitated by in- troducing a compression chamber into the descend- ng aorta. Pressure pulses were recorded from aorta, emoral artery, and the compression chamber. Pres- sure in the chamber begins to rise at the summit of he aortic pressure pulse, and rises and falls as a sine wave, which is of course quite different from the contour of the aortic pressure pulse. As pres- sure rises in the reservoir, the aortic pressure de- clines rapidly. The incisura is low and another defi- nite wave follows. The femoral pulse is of small amplitude and shows a marked dicrotic notch and wave.

It is pointed out that these results are contrary to what is expected from increased distensibility. Likewise there was no delay in pulse transmission. It is concluded that a common system is not pro- duced by insertion of the compression chamber. There are two systems of different natural frequen- cies. The chamber removes blood during the latter portion of systole and produces a negative arterial wave. Through reverberation a positive pressure wave is added to aortic and femoral pulses. Natural frequency of the arterial is virtually unchanged. The smaller pulse pressure is caused by the bigger capacity of the whole arterial system. It is not due to damping.

OPPENHEIMER

Rodbard, S., and Saiki, H.: Mechanism of Pressor Response to Increased Intracranial Pressure. Am. J. Physiol. **168:** 234 (Jan.), 1952.

The authors have undertaken an analysis of the blood pressure response to intracranial pressure in chickens. The effects of anoxia and asphyxia are produced slowly and are moderate in amount. The response to increased intracranial pressure is marked and rapid. During a bout of anoxia an increased cerebrospinal fluid pressure still produces its max- imal effect.

Evidently the response to increased intracranial pressure depends on factors other than hypoxia. Rises in intracranial pressure produce rises in blood pressure of almost equal magnitude. When the vagi are cut the pressor responses are increased. Short durations of elevated intracranial pressure (1 to 5 seconds) are followed by rises of almost equal mag- nitude. Negative intracranial pressure produces a fall in blood pressure.

The authors interpret these results as inconsistent with an anemic, anoxic or asphyxial etiology for the short hypertension following brief rises in intra- cranial pressure. They postulate intracranial pres- soreceptors (baroreceptors) which act as differential manometers registering the difference between in- travascular and intracranial pressures. A decrease in the difference elevates blood pressure by vaso- constriction, an increased difference lowers blood pressure.

OPPENHEIMER

PATHOLOGY

Swan, W. G. A., and Dewar, H. A.: The Heart in Hemochromatosis. Brit. Heart J. **14:** 117 (Jan.), 1952.

The authors review the literature and report two

additional instances of hemochromatosis. One occurred in a man of 32 who had recurrent retrosternal pain and an abnormal electrocardiogram characterized by elevation of ST and inversion of T in leads II and III. The other was in a man of 51 with signs of heart failure and with elevation of ST and coreshaped T in the electrocardiogram. Biopsy specimens from both showed hemochromatosis. The second one died. Histologic study of the myocardium showed patchy siderosis with the iron pigment present in the form of granules in the myocardial fibers. Fibrosis was most marked in those regions where pigmentation of muscle was most intense.

The authors believe that clinical evidence of heart failure in hemochromatosis is not infrequent. They believe that the extensive changes in the muscle adequately explain failure.

SOLOFF

Wilens, S. L.: The Nature of Intimal Thickening of Arteries. Am. J. Path. **27:** 825 (Oct.), 1951.

The focal character of the lesions of atherosclerosis is well recognized, but the writer presents evidence that lipid-containing blood plasma may gain entrance into the arterial intima in a uniformly dispersed state. The development in early life of a subendothelial fibrous zone occurs regularly and uniformly throughout the aorta and also throughout the large arteries. It is especially notable in those areas that are the future site of atherosclerosis. This thickening of the intima is progressive throughout life, and is more marked in men than in women. The marked development of this process is striking in male children, a fact first noted by Dock. Hypertension and diabetes both accelerate the development of intimal thickening so that it thus may exist before atheroma makes its appearance.

Intimal thickening is seen in laboratory animals, particularly in rabbits on a normal diet following forced cholesterol feeding. With the gradual disappearance of cholesterol, a fibrous thickening of the intima often develops. The process is not found in species that are resistant to spontaneous atherosclerosis. These observations suggest that the diffuse overgrowth of intimal tissue that occurs consistently in early life is not a natural developmental phenomenon, and that it is related in some way to the same mechanism that eventually leads to the formation of atherosclerosis. The writer also suggests that this process is a uniform one involving the entire intimal structure.

GOULEY

Symmers, W. St. C., and Gillett, R.: Polyarteritis Nodosa Associated with "Wire Loop Glomeruli." Arch. Path. **52:** 489 (Dec.), 1951.

A case is recorded with unusual contrasting vascular lesions, namely, polyarteritis nodosa and disseminated lupus erythematosus. A man, age 51 years, a known victim of tuberculosis with silicosis, was studied in a sanitorium and as an outpatient. He received no sulfonamides and no antisera. Satisfactory convalescence was rather abruptly altered by epigastric pain and malignant hypertension. Death was caused by recurring intestinal hemorrhages.

Microscopy revealed that the hemorrhage was due to perforation of an aneurysm into the duodenum. Moreover, there were numerous aneurysms in the viscera, especially in the spleen and liver some of enormous size. Microscopy revealed the lesions of polyarteritis nodosa; also platelet thrombi in capillaries, "wire loop" lesions in the renal glomeruli and acute hyaline necrosis of arterial walls as seen in lupus erythematosus. Pulmonary tuberculosis and silicosis were present, but in the opinion of the authors, without significant relationship to the vascular lesions.

GOULEY

Lansing, A. I.: The Role of Elastic Tissue in the Formation of Arteriosclerotic Lesion. Ann. Int. Med. **36:** 39 (Jan.), 1952.

Arteriosclerosis appears to be a dual process, involving aging of the arterial wall and cholesterol accumulation in the intima. Calcification of the senescent elastic tissue in the media occurs with or without atheromatosis. When the two coexist, analyses indicate that cholesterol accumulates in the intima plaque after the underlying media has undergone elastic tissue calcification. What factors condition the age change in chemical composition of elastic tissue remains to be determined. Although altered cholesterol metabolism may be a factor in arteriosclerosis, aging of the arterial wall establishes a substrate for penetration and accumulation of cholesterol. It is possible that, without such changes in the arterial wall, cholesterol will not accumulate in the lining of arteries.

WENDKOS

PHARMACOLOGY

Johnson, S. A. M., and Meyer, O. O.: The Treatment of Lupus Erythematosus Disseminatus with Cortisone. Am. J. M. Sc. **223:** 9 (Jan.), 1952.

Improvement in the signs and symptoms of lupus erythematosus occurred in nine cases treated with cortisone acetate. The patient received 6 Gm. of the drug either on a continuous schedule or in several courses with rest intervals. Upon discontinuance of therapy, the remission was not sustained in any instance. Cortisone, in several of the seriously ill patients, was apparently effective in tiding patients over acute pericarditic and cardiac complications.

The usual precautions of limiting the sodium intake and of adding 3 Gm. potassium chloride daily were followed to avoid some of the complications of such therapy; hirsutism, acne and thinning of the hair were noted. Ascites occurred in one patient while a toxic psychosis was precipitated in another.

The authors noted an increase in the leukocyte counts in some patients; however, a complete disappearance of lupus erythematosus cells from the bone marrow was not uniformly observed. Several patients in this group had previously received para-amino benzoic acid with some improvement which was not sustained and was less rapid than that obtained with cortisone.

SHUMAN

Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and Physiological Correlations in Patients with Mitral Stenosis. V. Am. Heart J. **43:** 2 (Jan.), 1952.

In this report, the authors attempt to correlate clinical findings in mitral stenosis with the degree of anatomic stenosis and with the severity of accompanying pulmonary vascular disease. The "constantly present" or "frequently recurrent" features in the clinical state of 30 patients with pure mitral stenosis were analyzed, and correlated with physiologic data. The authors have explained the clinical picture in mitral stenosis by the interplay of the degree of stenosis with the degree of pulmonary vascular obstruction. The role of the diseased myocardium was not considered. When the stenosis has advanced to a valve area of 1.0 square centimeter, an elevated pressure in the left atrium and pulmonary vasculature is required even at rest; and despite great increase in pressure, little increase in flow is possible. This area is a critical one, for at that level of stenosis, the pressure head needed to maintain a normal cardiac output approaches plasma osmotic pressure, and for unexplained reasons pulmonary vascular resistance increases. To some extent, the latter is a compensatory mechanism, protecting the pulmonary capillaries from a high hydrostatic pressure and pulmonary edema. The combination of a narrow valve with only a slight increase in pulmonary arteriolar resistance is associated with predominantly respiratory symptoms, exertional dyspnea, hemoptysis, and paroxysmal nocturnal dyspnea. The relatively strong right ventricle, unhampered by a high pulmonary arteriolar resistance, is able to congest the lungs acutely. The combination of a narrow valve, and moderate or great increase in pulmonary arteriolar resistance is associated with severe dyspnea, and right ventricular hypertrophy and failure. When the patients in this series were divided into four general categories based on the two factors, mitral valve area and pulmonary-arteriolar resistance, they showed common clinical patterns similar to the physiologic ones. There was some overlapping. Five cases did not fit well into these divisions.

HELLERSTEIN

Jawetz, E., Gunnison, J. B., and Speck, R. S.: Antibiotic Synergism and Antagonism. New England J. Med. **245:** 966 (Dec. 20), 1951.

Certain microbial infections no longer respond to a single antimicrobial agent. Under such circumstances it is well to take advantage of the synergistic action of certain combinations of chemotherapeutic drugs. The combined use of penicillin and streptomycin in the treatment of *Streptococcus fecalis* is an example. Most strains of staphylococci are said to have become relatively resistant. An example of bacterial endarteritis due to *Staphylococcus albus*, and successfully treated with terramycin and streptomycin, is described in detail. It is emphasized that such antibiotic mixtures should be used in correlation with etiologic diagnosis and test-tube evaluation by proper laboratory methods.

The antibiotic antagonism of penicillin and chloramphenicol, Aureomycin or terramycin in vitro and in certain experimental infections in mice is also described. It is pointed out that the interference is maximal when relatively small doses of the broad-spectrum antibiotics are added to penicillin. The interference results only in quantitative reduction of therapeutic efficacy, and it can be overcome by a large excess of any of the drugs involved. Further clinical observation will be required to determine the significance of antibiotic antagonism in the treatment of human disease.

ROSENBAUM

Cole, F.: Use of Human Serum Albumin in Cerebral Edema Following Cardiac Arrest. J. A. M. A. **147:** 1563 (Dec. 15), 1951.

The authors report a case of cardiac arrest occurring during spinal anesthesia in a 21 year old man undergoing hernioplasty. Cardiac massage was started within five minutes. Asystole was present for 11 minutes. Cerebral edema followed with coma, convulsions, cyanosis, hyperpyrexia, tachycardia, tachypnea, and insensitivity to light. Human serum albumin was administered intravenously three times in doses of 100 cc. (containing 25 Gm. of albumin). Recovery was complete within three weeks. The author feels that human serum albumin is a new weapon in the physician's armamentarium in the treatment of cardiac arrest and its sequelae.

KITCHELL

Ginsberg, V., Frank, N. F., and Gubner, R.: Procedure for Blood Transfusion in Heart Disease and in Elderly Subjects. J. A. M. A. **147:** 1656 (Dec. 22), 1951.

In situations requiring the transfusion of large amounts of blood, a practical difficulty is frequently imposed by associated disorders which restrict the ability of the heart to accomodate to an increased blood volume. The authors allow blood to sit in bottles in the refrigerator. After 48 hours the cells settle so that there is about 300 to 350 cc. of red blood cells to 250 to 300 cc. of plasma. With the aid of an empty vacuum bottle the plasma can be siphoned off in a few minutes, and the patient is ad-

ministered the sedimented blood with the use of gravity at an elevation of four feet by means of an 18 or 17 gage needle, while in the sitting position. The procedure reduces the total volume of fluid administered intravenously by practically one-half, and fully three-quarters of the sodium content of the transfused blood is eliminated. Administration of blood while the patient is in the seated position reduces the load on the heart.

KITCHELL

Hajdu, S., and Szent-Gyorgyi, A.: Action of DOCA and Serum on Frog Heart. Am. J. Physiol. **168:** 159 (Jan.), 1952.

Staircase is abolished by low temperatures and low potassium. Serum and desoxycorticosterone acetate produce similar reactions. The authors suggest that the specific action of desoxycorticosterone acetate influences contraction and staircase by modifying selective activity of the membrane. No direct interaction between desoxycorticosterone acetate and contractile proteins was demonstrated.

OPPENHEIMER

Yount, E. H., Rosenblum, M., and McMillan, R. L.: Use of Quinidine in Treatment of Chronic Auricular Fibrillation. Arch. Int. Med. **89:** 63 (Jan.), 1952.

In 155 unselected patients with chronic auricular fibrillation treated with quinidine, a normal rhythm was restored in 86 per cent of those who were given an adequate therapeutic trial. This was accomplished in an average of six days with a mean dose of 0.42 Gm. every four hours and a mean plasma quinidine concentration of 9.1 mg. per liter at the time of reversion.

The duration of fibrillation and the severity of the heart disease did not influence the results of treatment with quinidine. The patients of the oldest age group (70 to 86) responded most readily and to the smallest doses. The only underlying disease which appeared to affect the response to quinidine therapy was thyrotoxicosis; in patients with this condition restoration of normal rhythm was exceedingly difficult until the basic disorder was brought under control. Pharmacologic data obtained by the measurement of the plasma quinidine concentrations are presented as the basis for the establishment of a successful therapeutic regimen.

BERNSTEIN

PHYSICAL SIGNS

Koelsche, G. A.: Asthmatic Dyspnea. Proc. Staff Meet. Mayo Clin., **27:** 51 (Jan.), 1952

One distinguishing characteristic of asthmatic dyspnea is its tendency to occur in attacks. The duration of the attacks varies from one to several hours and in the uncomplicated case there is no discomfort or exertional dyspnea between attacks. Symptoms of asthmatic dyspnea help to distinguish it from other types. The first symptom is wheezing, then coughing either paroxysmal or almost incessant, and finally expectoration of a typically white thick gelatinous sputum. If blood is present in the sputum, it may indicate an associated obstructing lesion of a bronchus, such as carcinoma or bronchostenosis. Cyanosis and sweating are seen only if the asthmatic dyspnea is severe to extreme.

Finally, the almost invariable and remarkable relief which a small injection of epinephrine affords is characteristic of asthmatic dyspnea. Rest does not relieve an attack of asthmatic dyspnea, and consideration of factors which precipitate asthmatic dyspnea helps to distinguish it from other types.

SIMON

Gulotta, G. A.: A Proposed Method for Describing and Recording Auscultatory Findings. Bull. St. Francis San., **9:** 38 (Jan.), 1952.

A first heart sound is represented by the letter "S." The second heart sound is represented by the letter "D." A duplication of each one of these sounds is represented by a double "SS" or a double "DD." The third heart sound is represented by a small "d" and a gallop sound by a capital "G."

Systole is divided into three parts: early, mid and late; and in a like manner, diastole is also divided into three parts. The murmurs are graded according to Levine's classification, the grading being presented at the proper time interval.

Thus, for example, a grade VI early systolic murmur would be recorded as "S_{6o}"; a systolic murmur which occupies the entire duration of systole but which begins as a grade VI and in a decrescendo manner becomes grade II at the end of systole might be recorded as "S_{662}." If this murmur would be crescendo in type, it might be written as "S_{246}." The location of the gallop, or the third heart sound, is done in a similar manner. For example, a systolic gallop would be written as "SoGoD"; a mid-diastolic gallop would be written as "SoDoGo."

In this manner, a typical case of mitral stenosis and insufficiency, and ortic stenosis and insufficiency might appear on our record as (m) "$S_{342}D_{421}$"; (a) "$S_{444}D_{246}$; "(m)" stands for the auscultatory findings at the apex or mitral area and "(a)" for the auscultatory findings at the aortic area.

BERNSTEIN

PHYSIOLOGY

Linsada, A. A., Alimurung, M. M., and Lewis, L.: Mechanisms of Production of the First Heart Sound. Am. J. Physiol. **168:** 226, (Jan.), 1952.

The experiments of the authors suggest that the first heart sound results from a combination of muscular and valvular factors. A double vibration of the cardiac wall is produced when sudden changes in muscular tension activate the atrioventricular and in turn the semilunar valves. These are then transmitted to the chest wall. High and low pitched ele-

ments are included. Vibrations may arise in both valvular and muscular structures due to rapid changes in tension and pressure. Small vibrations which may be of muscular origin are sometimes noted between the two main groups of vibrations. Vascular vibrations are only found after ejection starts.

OPPENHEIMER

Youmans, W. B., Good, H. V., and Hewitt, A. F.: Cardio-inhibitory Response to Vasopressor Compounds in Rabbits with Sino-aortic Nerves Sectioned. Am. J. Physiol. **168:** 176 (Jan.), 1952.

In unanesthetized rabbits bilateral aortic nerve section and carotid sinus denervation reduce but do not entirely eliminate the cardioinhibitory response to pressor compounds. The remaining response is quite prominent and depends on depressor fibers of the intact vagi in the authors' opinion.

OPPENHEIMER

Youmans, W. B., Good, H. V., and Hewitt, A. F.: Inhibitory Effect of Vasopressin on Cardioaccelerator Mechanism After Sino-aortic Denervation. Am. J. Physiol. **168:** 182 (Jan.), 1952.

Cardioaccelerator activity is present at a high level after sinoaortic denervation. This activity is almost eliminated by Pitressin even though no known depressor pathways remain.

OPPENHEIMER

Frank, H. A., Frank, E. D., Jacob, S., Glotzer, P., Persky, L., Friedman, E. W., Schwartz, A., Rutenburg, A. M., Milrod, S., and Fine, J.: Traumatic Shock. XX. The Course of Hemorrhagic Shock in Dogs Treated by Peritoneal Irrigation or by an Artificial Kidney. Am. J. Physiol. **168:** 140 (Jan.), 1952.

The authors were unable to find evidence of a circulating toxin of etiologic importance in the shock condition. Dialysis was the technic employed. Tolerance to hemorrhagic hypotension was increased by peritoneal lavage. Some of the irrigating fluid is absorbed. Artificial kidney dialysis produced no pressor effect in dogs which were normal, nephrectomized, or in irreversible hemorrhagic shock.

OPPENHEIMER

Frank, H. A., Jacob, S., Friedman, E. W., Rutenburg, A. M., Glotzer, P. and Fine, J.: Traumatic Shock. XXII. Irreversibility of Hemorrhagic Shock and VDM Hypothesis. Failure of Ferritin to Affect Arterial Pressure and Survival Period of Hepatectomized-Nephrectomized Dogs.: Am. J. Physiol. **168:** 150 (Jan.), 1952.

Irreversible hemorrhagic shock was produced regularly in unmedicated dogs and those receiving a single dose (1 to 2 mg. per kilogram) of morphine. The authors suggest that since VDM is not found in absence of anesthesia or morphine, it is doubtful that it can account for development of irreversibility to transfusion in experimental hemorrhagic shock. Intravenous VDM did not change arterial blood pressure or survival, even though amounts used were in excess of those observed in advanced hemorrhagic shock and the animals were unable to inactivate or excrete VDM.

OPPENHEIMER

Ochsner, A., Jr.: Effects of Pulmonary Blood Flow and Distension on Capacity of Intrapulmonary Vessels. Am. J. Physiol. **168:** 200 (Jan.), 1952.

These studies appear to demonstrate that moderate degrees of positive lung inflation and negative pressure inflation both increase pulmonary vascular capacity. A given increase in blood flow increases intrapulmonary blood more at low flows.

OPPENHEIMER

Szent-György, A.: Contraction in the Heart Muscle Fibre. Bull. New York Acad. Med. **28:** 3 (Jan.), 1952.

The author discusses the physiologic and chemical factors in muscle contraction and points out that the basic mechanism of contraction in somatic and cardiac muscle is similar but the excitation initiating contraction differs. The contractile substance consists of myosin particles which are kept in proper alignment by a cloud of K^+ ions surrounding each molecule.

Contraction of the fiber results from precipitation of these protein particles and is associated with a wave of depolarization which travels along the membrane. The precipitation is due to the formation of a myosin-adenosine-triphosphate complex which unites with a precipitin, actin, to form a substance having two possible physical and energy-containing states depending upon its ionic charge. The intracellular ionic atmosphere is an important factor in regulating this phenomenon, since it decides the charges, the balance of forces, the union or dissolution of the actin-myosin complex and the tension developed in contraction.

Since cardiac muscle contraction is not initiated by the central nervous system the excitation for each contraction has to be generated by the muscle itself. Normally the excitatory impulses originate near the sinus and the depolarization generated becomes self-propagatory throughout the remainder of the heart. The proper timing and strength of the subsequent contraction depend upon the intracellular K ion concentration following each cardiac contraction. Normally it is decreased after a muscle contraction. The permeability of cardiac muscle cell membrane to the potassium discharged during a contraction is regulated by a sterol present in normal serum. With cardiac insufficiency this K balance is upset, the heart rate increases and the force of contraction is diminished.

The therapeutic action of the digitalis glycosides is probably explained by the fact that they act like

the normal serum regulating sterols and by replacing these normal regulating substances permit the heart to beat slowly and strongly again.

SAGALL

Swann, H. G., Hink, B. W., Koester, H., Moore, V., and Prine, J. M.: The Intrarenal Venous Pressure. Science **115**: 64 (Jan. 18), 1952.

The intrarenal interstitial pressure in dogs averages 25 mm. mercury. It was postulated that the pressure within capillaries and venules must exceed this pressure, and in order to test this hypothesis the authors measured the venous pressure above the epithelial lining of the renal pelvis. A long needle was thrust through the body wall into the vena cava opposite the entrance of the right renal vein. The needle is then inserted into the renal vein and a nylon catheter is run through the hilus and manipulated into an interlobar vein. In about half the tries the catheter readily slipped into an arcuate branch. This was confirmed at necropsy. The pressure here was found to be the same as the simultaneous intrarenal interstitial pressure. Both pressures increased during the peak of glucose or urea diuresis, and fell with pressor doses of epinephrine. On withdrawing the needle it was found that the pressure dropped abruptly when the tip reached the interlobar vein.

This confirms the hypothesis that the pressure in the renal venules and peritubular capillaries must be greater than 25 mm. The constriction of the arcuate-interlobar junction has the effect of keeping renal venous pressure higher than the intrarenal pressure.

WAIFE

ROENTGENOLOGY

Seaman, W. B., and Goldman, A.: Roentgen Aspects of Pulmonary Arteriovenous Fistula. Arch. Int. Med. **89**: 70 (Jan.), 1952.

The clinical features of cyanosis and clubbed fingers, associated with polycythemia and a pulmonary murmur, make the clinical syndrome of pulmonary arteriovenous fistula easily recognizable once the physician is aware of the entity. With the study of more cases it has become apparent that the classical clinical picture associated with a large pulmonary arteriovenous shunt and corresponding changes in the peripheral blood do not always occur. One or all of the prominent clinical manifestations may be absent, and the roentgen appearance may be the only positive finding leading to the correct diagnosis. Recognition of this anomaly is of the utmost importance, since it is surgically curable.

Experience with eight cases of pulmonary arteriovenous fistulae is reviewed for the purpose of determining the reliability of the diagnostic roentgen criteria for this condition. The role of fluoroscopic, laminagraphic, roentgen kymographic, and angiographic technics is discussed. Conventional roentgenograms supplemented by laminagrams should lead to the correct diagnosis in most instances. Angiography is of great value in demonstrating multiple lesions not discovered by other technics, and is to be recommended before surgical treatment is instituted.

BERNSTEIN

Levy, L., Fowler, R., Jacobs, H., Leckert, J., Irion, J., Rosen, I., and Chastant, H.: Angiocardiographic Confirmation of Pericardial Effusion. Am. Heart J. **43**: 59 (Jan.), 1952.

The authors present eight cases in which angiocardiograms were valuable in confirming or ruling out pericardial effusion. The presence of a large opaque shadow outside of the limits of the cardiac chambers suggests pericardial effusion or exudate and is rarely confused with cardiac hypertrophy. Small amounts of fluid usually cannot be determined accurately by angiocardiography.

HELLERSTEIN

Dusaillant, G., Lepe, A., and Gomez, G.: The Electrokymogram of the Left Ventricle and Auricle. Ventricular and Arterial Chronology in Normal Subjects. Acta cardiol. **7**: 38 (Fasc. 1), 1952.

The authors present the results of electrokymographic studies in 62 normal persons aged 17 to 42. Tracings of the left ventricular and auricular borders were recorded simultaneously with the pulse of the carotid artery, and with the electrocardiogram or phonocardiogram. The carotid sphygmogram was used as reference for the timing and the analysis of the electrokymogram.

Numerous variations were found of the contour and the chronologic appearance of the various segments of the left ventricular curve. By expressing the size of particular deflections as a percentage of the size of the total ventricular deflection, a method was developed for defining individual variations in numerical form, and, thus, determine limits of normal variations. Tracings obtained at the left atrial border also showed great variations, and occasionally had the contour described for mitral insufficiency. This, however, was never a constant finding in normal individuals.

In view of the many technical details involved and the numerous variations of normal patterns, the authors feel that, at the present stage of development, the method is only of limited value.

PICK

Heckmann, K.: Studies of Cardiac Pulsations with the Help of Electrokymography and Phasic Analysis. Zschr. Kreislaufforsch. **41**: 2 (Jan.), 1952.

The author claims priority in the development of electrokymography in 1936. He has now developed a method for integration of the various types of pulsation observed at identical and successive time intervals over different portions of the heart border. By drawing upon an orthodiagram the size of the

various synchronized deflections, obtained in the electrokymogram at various levels, and by connecting the endpoints of these markings, the contour of the heart shadow during successive phases of contraction and relaxation can be precisely outlined.

By this method, which the author calls phasic analysis, it could be shown that the centripetal motion does not start simultaneously along the left ventricular border, indicating latency of certain parts, probably due to the complicated architecture of the myocardium. In pathologic cases the author found several types of localized abnormal pulsations opposite in direction to normal movements seen during systole and diastole. In extreme instances of myocardial damage, as in myocardial infarction, bulging out of the apical portion can be reconstructed by the author's method. In other instances of severe myocardial damage, diastolic collapse of cranial portions of the left ventricle was clearly demonstrated.

PICK

Levy, L., II, Fowler, R., Jacobs, H., Leckert, J., Irion, J., Rosen, I., and Chastant, H.: Angiocardiographic Confirmation of Pericardial Effusion. Am. Heart J. **43**: 59 (Jan.), 1952.

The authors presented the data obtained on patients with pericardial effusion, using angiocardiography. By outlining the right cardiac chambers through the use of a relatively small amount of contrast medium, they were able to obtain diagnostic films.

It was concluded that angiocardiography is of value in making the diagnosis of pericardial effusion in those cases in which this state is not associated with the classic signs of cardiac compression, or in differentiating this condition from a dilated heart.

ABRAMSON

Smith, P. G., Rush, T. W., and Evans, A. T.: The Technique of Translumbar Arteriography. J. A. M. A. **148**: 255 (Jan. 26), 1952.

The authors report they have performed over 1,000 aortic punctures without a fatality and without significant morbidity. Translumbar arteriography is useful for differentiation between renal tumors and cysts. The technic may conclusively demonstrate the potential function of a kidney whose ureter is obstructed when intravenous pyelogram has failed to demonstrate its status. Ischemia of one kidney by arteriography should be demonstrated before doing nephrectomy in treatment of the Goldblatt type of hypertension. The procedure is quite safe if precautions are used as outlined.

It is a valuable instrument in diagnosing the following lesions relating to the kidney: hypertension, hydronephrosis, neoplasm, cyst, anomalies, aberrant arteries, extrarenal retroperitoneal masses, hypoplasia, atrophy and agenesis. There may be definite value in disclosing vascular conditions of the splenic, hepatic, gastric, aortic, renal, iliac, and even femoral and popliteal arteries. The procedure has also been used to localize placental position in ruling out placenta previa.

KITCHELL

SURGERY IN HEART AND VASCULAR SYSTEM

Murray, G.: The Surgical Treatment of Mitral Stenosis. Canadian M. A. J. **65**: 307 (Oct.), 1951.

Of 37 mitral valves operated upon, the mortality rate has been about 20 per cent. Fifty-five per cent of all operated upon have what might be termed fairly good results, with ability to return to some sort of work. Another 25 per cent have improved, gone to work and done fairly well for a time. But within a period of from four to six months, many have relapsed into failure, and many of these have died.

The remaining 20 per cent have survived operation but, within a matter of a few hours or a few days, have manifested increasing difficulty and have not survived. Those with massive auricular thrombi have been in this group and some have been shown to have irreversible changes in the pulmonary tree If the proper patients can be selected, then surgical treatment offers them considerable improvement, for the present at least. How long these results will last, whether the disease will reactivate and heal up the incisions made in valves, or what the end result may be are unknown.

BERNSTEIN

Shafiroff, B. G. P., Baron, H. C., and Kau, Q. Y.: The Use of Auricular Appendage as an Autogenous Myocardial Graft. J. Thoracic Surg. **22**: 631 (Dec.), 1951.

Free grafts of auricular appendage were transplanted on the normal or surgically altered hearts of 18 dogs, and the regenerative capacity of the tissues was studied after a fixed lapse of time. In some cases the auricular appendage was excised and transplanted upon the normal ventricular myocardium of the same animal, while in others it was placed over a segment of ventricle which had been rendered ischemic by ligation of a peripheral branch of the coronary artery. In a third group, a full thickness segment of ventricle was excised and the wound closed with the interposition of the auricular graft.

After a 10-week postoperative observation period, the majority of the grafts in the three groups, although markedly reduced in size, showed firm and continuous union with the subjacent recipient ventricular myocardium.

On the basis of the results, the possibility of using autoplastic grafts in human cardiovascular surgery was suggested.

ABRAMSON

Overholt, R. H., Burwell, C. S., Woodbury, J. W., and Walker, J. H.: Constrictive Pericarditis and

Constrictive Pleuritis Treated by Pericardiectomy and Pulmonary Decortication. J. Thoracic Surg. **23:** 1 (Jan.), 1952.

The authors presented a case of combined constrictive pericarditis and constrictive pleuritis which was treated surgically. The cause of the condition was a crushing injury to the chest which produced an uninfected bilateral hemothorax and hemopericardium.

Decortication of the left ventricle was performed and the apex was freed, followed by bilateral pulmonary decortication. The postoperative course was uncomplicated.

ABRAMSON

Smith, R. G., Gullickson, M., and Campbell, D. A.: Some Limitations of Lumbar Sympathectomy in Arteriosclerosis Obliterans. Early Results in One Hundred Consecutive Cases. Arch. Surg. **64:** 103 (Jan.), 1952.

The authors studied the effect of lumbar sympathectomy on patients with arteriosclerosis obliterans. In the series only six patients were operated on for prophylactic reasons, while in the remaining 94 extremities advanced complications were present. Three patients died after operation, two of pneumonia and one as a result of thrombosis of the abdominal aorta.

Following surgery there was a significant relief of intermittent claudication in 10 extremities and of pain in 21 extremities. Nine limbs with ulceration healed (33 per cent). In the presence of gangrene, no extremity was saved in which the femoral or popliteal artery was occluded, while there was a salvage rate of 75 per cent in those cases in which there was at least one patent major artery below the knee.

In patients with major arterial occlusion, marked edema of the extremity, constant severe rest pain, and intermittent claudication, sympathectomy did not permanently alter the clinical picture in any instance. The severe pain and subsequent progressive gangrene necessitated amputation of the extremity within several weeks or months.

The authors concluded that sympathectomy holds little or no promise of saving an extremity if an actual drop in skin temperature of the toes occurs after lumbar sympathetic block. Furthermore, its use is limited in the presence of gangrene.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Muirhead, E. E., Montgomery, P. O'B., and Gordon, C. E.: Thromboembolic Pulmonary Vascular Sclerosis. Arch. Int. Med. **89:** 41 (Jan.), 1952.

Two cases of Ayerza's syndrome with common pulmonary morphologic features are presented. The pulmonary vascular sclerosis (endarteritis) depicted may have been considered of the primary type were it not for the presence of numerous occlusive masses within small pulmonary arteries. These occlusive masses in the first case were either embolic or thrombotic. In the second case the masses appeared to be proteinaceous. This patient had a marked hyperglobulinemia, cryoglobulinemia, plasmacytosis, and glomerulitis. This represents the first instance recorded of cryoglobulinemia with pulmonary vascular sclerosis.

There is a growing body of evidence supporting the view that occlusive masses in small pulmonary arteries cause pulmonary vascular sclerosis. This explanation is preferred for the cases reported herein. The term "thromboembolic pulmonary endarteritis" is suggested for this form of pulmonary vascular sclerosis. Although pulmonary hypertension has been considered as the cause of pulmonary endarteritis, it appears as plausible that alterations in the nutritional status of the arterial wall are of fundamental importance. Such a hypothesis considers the hypertension, when present, as a by-product of the vascular occlusion and relates the sclerosis to the injury plus the operation of the repair process as it affects blood vessels.

BERNSTEIN

Appel, W., and Rohrl, W.: Thrombosis of the Pulmonary Artery. Aerztl. Wchnschr. **6:** 1161 (Dec.), 1951.

The authors report clinical observations in four cases which in their opinion are sufficient to establish the diagnosis of thrombosis of the pulmonary artery. Two of the cases died and at autopsy multiple and partly organized pulmonary emboli of varying age and size were found. There was, however, no sign of pulmonary infarction.

The authors consider the main characteristic clinical signs of the syndrome to be repeated attacks of cardiovascular collapse, onset of unexplained and untreatable right heart failure, accentuation of the second pulmonic sound, and electrocardiographic changes indicating cor pulmonale. Roentgenologic examination shows enlargement of the shadow of the right pulmonary artery with circumscribed areas of diminished pulsation (seen in kymograms), if the thrombosis involves a larger segment of the artery. The etiologic factor of the syndrome is either secondary thrombus formation following nonfatal pulmonary embolism, or primary thrombosis of a pulmonary artery on the basis of inflammation of the vascular wall.

PICK

VASCULAR DISEASE

Jonnart, L., Lequime, J., and Denolin, H.: Experimental Investigations in Chronic Peripheral Arterio-Venous Aneurysms. Acta cardiol. **7:** 16 (Fasc. 1), 1952.

The authors studied changes of the circulation brought about by compressing and opening a large arteriovenous fistula. The experiments were per-

formed on unanesthetized dogs, three weeks to six months after an anastomosis had been established between femoral artery and vein. Cardiac output was determined with the help of cardiac catheterization, and pressures in both femoral arteries were recorded after cannulation of the vessels. In some experiments the pressure gradient between the arterial and venous portion of the aneurysm could be determined by advancing the catheter from the right auricle through the inferior vena cava down to the site of the lesion in the femoral vein.

On sudden release of compression of the arteriovenous fistula, a complex reaction takes place. First, lowered arterial resistance results in a passive drop of systolic and diastolic arterial pressure, which is succeeded by a two stage adaptation reaction. The first and immediate stage is mediated over the carotid sinus reflex and consists in tachycardia with more complete systolic emptying of the ventricles. The second stage which is delayed for several seconds is characterized by systemic vasoconstriction and a rise in cardiac output in accordance with Starling's law. As the systemic pressure rises, the tachycardia diminishes, until, following some oscillations, final equilibrium is established. A reverse order of events can be observed following compression of the fistula.

PICK

Shedd, D. P., Alley, R. D., and Lindskog, G. E.: Observations on the Hemodynamics of Bronchial-Pulmonary Vascular Communications. J. Thoracic Surg. **22:** 537 (Nov.), 1951.

The authors studied the vascular pressure changes in the lungs of dogs on occluding the pulmonary artery and vein. The procedure was carried out by means of a snare cannula around the left lower lobe pulmonary artery and vein.

Occlusion of a lobar vein alone caused an immediate moderate rise of intravascular pressure within the lobe, with a return to normal upon release of the vessel. Obstruction of a lobar artery alone by intraluminal balloon or perivascular snare caused a prompt drop of pressure within the lobe. Occlusion of both vessels simultaneously was followed by a marked rise of pressure, greater than that observed with obstruction of the vein alone.

It was believed that the rise observed within the pulmonary vascular bed with occlusion of both artery and vein was due to active congestion produced via the bronchial arteries. Evidently the poorly developed bronchial veins were inadequate to accommodate more than one third of the blood delivered by the bronchial arteries in unit time.

The suggestion was made that the communications between the bronchial and pulmonary arteries at the precapillary level probably play an important role in the fate of a pulmonary segment or lobe which has been deprived of its direct pulmonary arterial blood supply by an embolus. If such a segment has a high degree of functional venous obstruction, as from chronic passive congestion or mitral stenosis, it is conceivable that bronchial collateral inflow at systemic pressures would produce a destructive imbalance, tending to favor the development of capillary engorgement, increased filtration, edema of the alveoli and interstitial tissues, diapedesis, and frank hemorrhage.

ABRAMSON

OTHER SUBJECTS

Helmholz, H. F.: Laboratory Studies of Patients Whose Chief Complaint Is Dyspnea. Proc. Staff Meet., Mayo Clin. **27:** 61 (Jan.), 1952.

Tracings of vital capacity, maximal inspiratory capacity and maximal breathing capacity for patients who complained of dyspnea often show characteristic patterns when compared with those of a normal person.

The series of tests enumerated, in which estimations are made of certain characteristics of the pulmonary ventilation system and of the oxygen saturation of hemoglobin in arterial blood under several different conditions, are valuable in clarifying the cause of dyspnea. It should be emphasized that in many cases results of the tests will not fit any of these pictures. Pulmonary edema will cause a decrease in oxygen saturation which will be accentuated by any exercise. Venous arterial shunts will often give findings similar to the case of diffuse fibrosis. Circulatory failure can be the main factor in any case of inefficient ventilation of the lungs. In such cases, these tests alone can be misleading unless the results are interpreted with all other findings.

SIMON

BOOK REVIEWS

The Auricular Arrhythmias. *Myron Prinzmetal, M.D., Eliot Corday, M.D., Isidor C. Brill, M.D., Robert W. Oblath, M.D., and H. E. Kruger, and 8 associate editors.* Springfield, Ill., Charles C Thomas, 1952. 398 pages, 514 figures (22 in full color). $16.50.

In attempting to make an electrocardiographic differentiation between auricular tachycardia and some types of auricular flutter, the authors apparently have had the same difficulties as other electrocardiographers have had in the past. They decided however, very commendably, to do something about it. The result has been a compilation of their rather exhaustive observations both clinical and experimental on four dysrhythmias: the auricular premature systole, auricular tachycardia, auricular flutter, and auricular fibrillation. The scope of the book can be judged from the length of the bibliography which has 686 listings.

The mechanical behavior of the auricles during the artificially produced arrhythmias was observed by means of high speed cinematography in color. Some of the stills are reproduced from these movies. The electrical behavior was studied both directly and indirectly by means of direct-writing electrocardiographs but in some instances also with the more precise cathode ray oscillograph coupled to preamplifiers of known frequency characteristics. Most of the experimental observations were made on dogs; 18 were made on man during mechanical stimulation of the auricles in the course of various thoracic surgical procedures.

The general conclusion reached is that the four auricular arrhythmias have a unitary nature. Each is regarded as resulting from discharge of a single heterogenetic focus in the auricles; the different electrocardiographic appearances are ascribed principally to different rates of discharge of this focus. This unitary theory denies the existence of circus rhythm. Many of the data and arguments presented by the authors seem valid and cogent; some are not. In any case, all of them are provocative.

It is difficult in reviewing the book not to offer some defense for Sir Thomas Lewis who seems to be on the wrong side of things in many of the chapters. Although the present authors state that they repeated Lewis' experiment exactly, the truth is that only in five dogs was this done. Even in these the instrumentation and the electrodes used were different from and probably less exact than those used by the original investigator. Apparently the authors had the same difficulties producing post-faradization or post stimulation auricular flutter as did Lewis because the remarks on this type are sparse and not too clear. For the most part they produced flutter with aconite, a stimulant which continued to act throughout each experiment. Lewis' circus rhythm theory was based on observations of a rhythm which occurred as an *aftereffect* of an electrical stimulus. In a control study he made observations on three dogs during *continued* electrical stimulation and obtained results quite different from those in the poststimulation experiments. Therefore, it is possible that Lewis and the present authors have made observations really on two different types of electrical phenomena in the heart which each has labelled auricular flutter.

There are some other points which can be questioned but the reader will want to pass judgement on these for himself. Considered collectively they keep the door on circus rhythm open.

The usefulness of the high speed cinematographic method for observing surface motion of the cardiac chambers seems established, but one wonders about the adverse effects of the intense heat generated by the necessary close-up lighting even during very short exposures. In several places the authors speak of the "efficiency" of the auricles as determined from simple observation of the surface movements. If one is accustomed to thinking of efficiency in terms of the laws of thermodynamics, such deductions seem quite gross.

The chapters on pharmacology and treatment of the auricular rhythms are complete and informative.

The authors are to be congratulated for challenging a theory never adequately substantiated by fact. Every student of cardiac rhythms and all those interested in electrocardiographic theory will want to read this book carefully and critically.

CHARLES E. KOSSMANN

Roentgenology of the Heart and Great Vessels. *Harry E. Ungerleider and Richard Gubner.* New York, The Equitable Life Assurance Society of the United States. (Reprinted from *W. D. Stroud:* **Diagnosis and Treatment of Cardiovascular Disease,** ed. 3. Philadelphia, F. A. Davis, 1950.) 109 pages, 102 figures.

The authors originally prepared this work as a chapter for *Diagnosis and Treatment of Cardiovascular Disease* (Stroud). As such, the emphasis throughout has been on the fundamentals of cardiac fluoroscopy and roentgenography. In a concise manual of a little over 100 pages, they have presented a thorough discussion of the various phases of cardioroentgenology, well illustrated by numerous diagrams and roentgenograms. The manual is divided into four basic considerations: (1) methods of examination, (2) evaluation of cardiac and aortic measurements, (3) roentgenology of the normal

heart, and (4) roentgenology of the abnormal heart. The latter section is divided into two parts: the roentgenology of the heart (1) in acquired disease, and (2) in congenital heart disease.

To be particularly recommended is the discussion and evaluation of cardiac and aortic measurements as applied to heart disease. The authors have had an unusual experience in this field through their work in the Medical Department of the Equitable Life Assurance Society. They have shown conclusively that the measurement of greatest practical significance in daily work is the transverse diameter of the heart compared with normal standards based on the height and weight of the patient. They point out again that the so-called cardiothoracic ratio, in which the transverse diameter of the heart is compared with the transverse diameter of the chest, is a very inaccurate measurement.

This reviewer regrets that the authors have not seen fit to include a discussion of the hazards of fluoroscopy and their avoidance by the use of small fluoroscopic fields, short times of examination and protection of the fluoroscopist by apron and gloves. This is particularly important in view of the fact that most cardiologists are not trained in the physics of x-ray and hence, as a rule, are not as aware of danger as are radiologists. The discussion of congenital heart disease is necessarily brief and for the interested reader this presentation is only a guide to further study. The newer technic of angiocardiography is not fully covered. The other sections are quite complete and should be read with careful attention to the details since, in view of the brevity of the presentation, each sentence is of significance in the consideration of the whole.

This manual is recommended as an excellent presentation of the fundamentals of cardioroentgenology and as an introduction to this rapidly expanding and significant field. It should prove of particular value to the medical student and beginner in the field of cardioroentgenology.

HERMAN W. OSTRUM

Some Historical Notes Upon the Reappearance of a Magnificent Book

Anyone who is tempted to read the following report should be warned at the outset that it is emphatically not a formal book review. It is, rather, a very personal account of some events leading up to the republication of a volume that has meant much to me and my friends, events in which I played an unexpected and innocently decisive role. As soon as the book had been republished I asked for the privilege of writing a memorandum upon it for possible insertion in CIRCULATION. This was granted by the publisher, though not without considerable and understandable hesitation. The paragraphs below were written at once, but caused him acute unhappiness and embarrassment, since he feared that their publication might subject him to charges of immodesty and self-advertising. However, he recognized with relief that this decision rested in the hands of the Editor and members of the Editorial Board, who agreed that the world would probably continue on its way undisturbed even if CIRCULATION should publish a commentary somewhat more personal than the usual book review. Inasmuch as the author of the book is among my cherished friends, and since I asked to be allowed to write this account, all blame, discredit, and adverse criticism should fall upon my head, which may become bloody but will remain unbowed.

At the close of the 1951 annual session of the American Heart Association in Atlantic City there was a joint celebration of three important birthdays: the first of CIRCULATION, the tenth of the firm of Grune & Stratton, and the fiftieth of Henry M. Stratton. Mr. Stratton, being a genial, generous, gregarious soul, decided to honor the occasion by giving a dinner for a small fraction of his innumerable friends. Not content to minister to their physical needs only, he thoughtfully provided intellectual fodder also. Three distinguished guests who are also among his warm friends were asked to speak briefly upon three phases of education, this being the field of human endeavor to which he has devoted most of his abounding energy. At almost the last moment it was realized that no one had been selected to act as master of ceremonies and introduce the speakers, and this pleasant assignment was offered to me. It was accepted instantly and gratefully, with the one stipulation that no speech would be required.

About a third of the invited guests could not attend because their trains and planes were delayed by several days of continuous rain, but some fifty gathered at the appointed hour and did full justice to the delectable food and drink. Then they listened with appreciation and in complete absorption while Dr. Samuel Proger outlined some of his exciting ideas about revision of medical education, Dr. Irving Wright spoke forcefully and thoughtfully about the influence and methods of the press in educating the public upon medical matters, and Dr. William Dameshek told charmingly of the early days of his friendship with Mr. Stratton.

During the several hours immediately before the dinner, I had become increasingly discontented with my assignment of merely introducing the three speakers. It seemed desirable that there should be an epilogue, a brief commentary that would be consonant with the preceding talks and at the same time a suitable word of farewell. In pondering the fitness of such a plan, it suddenly occurred to me that there was on my bedside table a book of which almost any page or chapter would be singularly appropriate for this purpose. A few passages from several chapters were hurriedly marked, one of the hotel stenographers kindly typed them for me, and

they were read as the concluding item on a program that had been most delightful.

The response of the audience, although not wholly unexpected, was rather overwhelming. About two-thirds of those present expressed their delight at the deep thoughtfulness and eloquence of the several pages that had been read, and a great many demanded the name of the volume and the author, declaring that they must secure copies at once. Among the most enthusiastic and clamorous was our host, who, upon learning that the book was out of print, declared with fervor: "It can't be! It's impossible that a book such as that could be allowed to go out of print. If the publishers refuse to reprint it, tell the author that I will gladly bring out a new edition." I hastened to inform the author of this exciting development, but his own absence from home and Mr. Stratton's wanderings through Europe delayed the negotiations and preparations, so the new volume did not appear until 1952.

This book was not written primarily for physicians, as indicated by the fact that its chapters appeared originally in such magazines as *Harper's*, *The Yale Review*, and *The American Mercury*. My own experience with nonmedical friends has shown conclusively that enthusiasm for it is by no means limited to doctors. But since most of my closest friends *are* doctors, the majority of them in the cardiovascular field, it is not surprising that my enthusiasm for this volume has been shared with many of these. It should mean a great deal to most readers of this commentary to learn that the book has been read, admired, and cherished by Drs. Edgar Allen, Arlie Barnes, William Bunn, Charles Connor, Tinsley Harrison, Duckett Jones, Thomas McMillan, Hugh Morgan, Irvine Page, David Rutstein, Roy Scott, and Irving Wright. To say that men of such varied tastes, such distinction and high intelligence, have all found in its pages eloquence, beauty, and thoughtfulness is to say much. This list will soon be longer, for other friends will receive copies now that they have become available again.

This is a personal confession, not a formal review. Indeed, it would be impossible for me to comment intelligently upon the technical basis of these fascinating chapters, since they were written from the standpoint of a geologist and paleontologist. But a knowledge of those fields is not necessary for full understanding and appreciation, since the author is a master in the art of presenting his materials and thoughts lucidly and eloquently. Thousands have recently found great enjoyment in reading *The Sea Around Us*, without feeling the need for a detailed knowledge of oceanography. The subject of the present commentary was written with the same beauty, clarity, and obvious mastery of the basic science from which the thoughts and deductions were drawn. But in fairness to the author let me quote several sentences from the introductory chapter.

"The tendency to accept easy and pleasant answers for difficult and disagreeable problems is one of the perennial temptations of man. But there will always be those who are temperamentally barred from the bliss of wishful thinking. They will prefer to plod toward truth, however slowly, with the help of observation, measurement, experiment, and induction, distrustful of wings that might melt away in the sun. . . . While the fundamental mystery of life remains as mysterious as ever, the manifestations of living are each year becoming better known. Each year the light of scientific inquisitiveness illumines more brightly not only the creatures of today but also those of many a lengthy yesterday. For life left a trail in the mud of the past which grew more distinct as the eons slipped away. To retrace its devious windings is to relive the most exciting drama ever enacted in the theatre of time. It is also to wonder what the drama means. The student of earth history sees in retrospect what could never have been foretold. . . . If there is any meaning for mice or men in the restless drive of life, a billion years of living should contain it. To search those years for that meaning will be the object of this book."

The title of the book? It is *Patterns of Survival—An Anatomy of Life*,* by John H. Bradley. Those who have read and admired it as I have will understand why I wanted to write this personal note about it. These words are addressed to my past, present, and future friends who have not yet read it, in the sincere belief that they will be glad to know of its existence. To me it seems a book for all who find joy, deep satisfaction, a lifting of the heart and strengthening of the spirit in wise, thoughtful reflections upon man's heritage, expressed in words of great beauty.

H. M. Marvin

* New York, Grune & Stratton, 1952. 231 pages. $3.75.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone GRamercy 7-9170

DR. WRIGHT'S MESSAGE TO INTER-AMERICAN CONGRESS

Dr. Irving S. Wright, President of the American Heart Association, speaking at the convocation ceremonies opening the Inter-American Congress of Cardiology in Buenos Aires on August 30, stressed the need for closer rapport between scientists.

"In spite of the tremendous development of the technics of communication," Dr. Wright pointed out, "unfortunately the millenium of understanding is not yet at hand. Familiarity with scientists at their conferences and with scientific literature reveals that the misunderstandings and the failures to confirm the works of others frequently rests on failure in communication. This problem is markedly increased by language barriers and the fact that exact scientific translation often becomes all but impossible."

Dr. Wright enumerated the following five points to help improve relations between scientists:

"1. Continue the efforts toward good will and friendship among all the people on this earth,

"2. exert constant effort toward the development of better methods of communication between scientists, and especially between those for whom a language barrier presents added difficulties,

"3. provide by example and constant effort, standards of individual conscience and integrity which will shine as a light to all other scientists and in particular to those young minds who will be influenced by our example as they enter this old and honored estate,

"4. provide leadership in the fields of basic and clinical research in the field of diseases of the heart and blood vessels, and

"5. provide farseeing and sound guidance in those aspects of social consciousness which apply to problems of health in the field of cardiovascular diseases."

RULES FOR HOWARD W. BLAKESLEE AWARD

The Howard W. Blakeslee Award of the American Heart Association, recently established to encourage high standards of scientific reporting on cardiovascular diseases, has been set in the amount of $1,000. In releasing the rules of the competition, H. M. Marvin, M.D., chairman of the Awards Committee, said the award would be given annually to the individual whose creative efforts have contributed most toward public understanding of the cardiovascular diseases in any medium of communication—including newspapers, magazines, books, radio, television or films.

Material published or produced during the 1952 calendar year is eligible for consideration. Entries must be postmarked not later than Jan. 15, 1953. The winner will be announced at the annual meeting of the American Heart Association, to be held in April, 1953, in Atlantic City.

The award was made possible through funds contributed by the Industrial Publishing Company of Cleveland and the Robert Z. Greene Foundation of New York City.

Persons other than the authors may present entries for consideration. Entry blanks and further information may be obtained from the Chairman, Managing Committee, Howard W. Blakeslee Award, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

FELLOWSHIP IN PEDIATRIC CARDIOLOGY

Applications are now being accepted for a Fellowship in Pediatric Cardiology at the University of Utah, which will begin in July, 1953. Applicants may write directly to Hans H. Hecht, M.D., Associate Professor of Medicine, Salt Lake General Hospital, 175 East 21st South Street, Salt Lake City 15, Utah.

PUBLIC HEALTH DIVISION

The Public Health Division of the Association announces that Miss Dorothy Schober, formerly Heart Work consultant with the New York State Committee on Tuberculosis and Public Health of the State Charities Aid Association, has joined the staff as a Program Consultant. Mr. S. S. Lifson, Director of Program Development for the past three and a half years, has become Director of Health Education Service for the National Tuberculosis Association. James H. Stone, formerly Program Consultant in the Public Health Division, has become Executive Director of the Virginia Heart Association.

REMINDER NOTICES

Grants-in-Aid Applications Due

Applications for research grants-in-aid for the fiscal year 1953–54 should be forwarded to the Medical Director of the American Heart Association, postmarked not later than *Dec. 1, 1952.*

Manuscripts for "Circulation Research"

The editors of Circulation Research are now considering manuscripts for the Association's new bimonthly scientific journal, which will be devoted exclusively to basic research. The editors are also interested in preliminary reports of significant current research advances. Such reports will be a regular feature and should not exceed 500 words.

Material will be restricted to new research data which have not been, and will not be, published elsewhere, and should be sent to Dr. Carl J. Wiggers, Editor, Circulation Research, 2109 Adelbert Road, Cleveland 6, Ohio. The new journal will begin publication in January, 1953.

Subscription Rates to "Circulation Research"

Research Journal Membership-Subscriptions, available through the Association and most of its affiliates, include the monthly bulletin, *Modern Concepts of Cardiovascular Disease*, and admission to the Association's annual Scientific Sessions.

The annual rates are as follows:

Research Journal Membership-Subscription..... $9.50
(In Canada and foreign countries $10.50)

Combined Journal Membership-Subscriptions, Circulation and Circulation-Research..... $19.50
(In Canada and foreign countries $21.50)

Special Rate:

Persons engaged in full-time research may, upon application, obtain for their own personal use a subscription to Circulation Research for $6.00 or a Research Journal Membership-Subscription, including Association membership privileges, for $8.00.

(Direct subscription to Circulation Research is available from the publisher, Grune and Stratton, Inc., at $7.50 per year, but does not include Association membership privileges.)

Papers for the Scientific Sessions

All those desiring to present papers at the Association's Scientific Sessions should submit abstracts *in triplicate* of the proposed presentation to Dr. André Cournand, Chairman of the Program Committee, % American Heart Association, 44 East 23rd Street, New York 10, N. Y., not later than *Jan. 1, 1953.* Abstracts should not be longer than 300 words and must contain in summary form, a specific statement of the results obtained or conclusions reached (not merely a statement that results on conclusions will be presented or discussed at the meeting).

CALENDER

Nov. 9–10: American Society for the Study of Arteriosclerosis, Hotel Knickerbocker, Chicago, Ill.

Nov. 10–12: Association of American Medical Colleges, 63rd Annual Meeting, Hotel Broadmoor, Colorado Springs, Colo. Dean F. Smiley, M.D., Secretary, 185 North Wabash Avenue, Chicago 1, Ill.

Nov. 10–13: International Medical Assembly, Postgraduate School of Interstate Postgraduate Medical Association of North America, Public Auditorium, Cleveland, Ohio.

Dec. 2–5: Sixth Annual Clinical Session of American Medical Association, Denver, Colo. (Will feature review lectures and panels on current progress in cardiovascular diseases.)

Apr. 8–12: **Twenty-Ninth Annual Meeting, American Heart Association,** Hotel Chelsea, Atlantic City, N. J.

Apr. 9–12: **Twenty-Sixth Scientific Sessions, American Heart Association,** Hotel Chelsea, Atlantic City, N. J.